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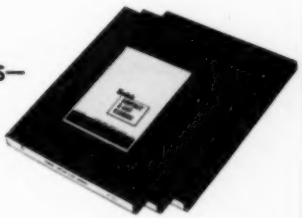

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DISSEMINATED PULMONARY CALCIFICATION[1,2]

A Report of 114 Cases with Observations of an Antecedent Pulmonary Disease in 15 Individuals

F. CLARK WHITE AND HARRY E. HILL

(Received for publication December 9, 1949).

The relatively frequent occurrence of disseminated pulmonary calcification in the northeastern part of the state of New York calls for attention, since most of the previously reported cases of this type of calcification have been found in the central (1) or eastern central (2, 3) region of the United States. It is of interest, therefore, that during a period of five years a total of 114 patients have been discovered with definite evidence of a disseminated type of pulmonary calcification in the Ray Brook State Tuberculosis Hospital District.[3] The significance of these cases is enhanced by the fact that in 15 patients it has been possible to observe clinically, as well as roentgenographically, the development of a chronic pulmonary disease from the onset to the end stage of disseminated pulmonary calcification.

The etiology of this disease has long been an enigma. Some investigators ascribed the calcification to healed miliary tuberculosis (4–10) or tuberculous bronchopneumonia (10), while others considered it the result of a disturbance of calcium metabolism (11) or a fungus disease (1). The histopathologic investigations of Geever (12) and Riley (13) failed to clarify the etiologic nature of the disease. Except for isolated observations (14–17, 42), there have been no descriptions of a pulmonary disease which precedes disseminated pulmonary calcification with observations from the onset of the disease to the stage of widely scattered calcifications.

A contribution to a better understanding of the etiologic problems of pulmonary calcification was made by the recent observations (18–24) that in certain regions many individuals with such calcification did not react to tuberculin. As a result, the widely held concept of a tuberculous infection as the basis of pulmonary calcification gave way to a search for a nontuberculous agent. There

[1] From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

[2] Presented at a meeting of the New York State Epidemiological Society, October 24, 1949, New York City.

[3] The Ray Brook State Tuberculosis Hospital District comprises the counties of Clinton, Essex, Franklin, Hamilton, and St. Lawrence.

are indications (25, 26) that, in areas where coccidioidomycosis is endemic, pulmonary calcification seems to be related to previous infection with this fungus. Ascariasis was considered as an etiologic factor by other workers (27), although they were unable to substantiate the significance of this condition with respect to calcification in man.

In 1945, a relationship between nontuberculous pulmonary calcification and skin sensitivity to histoplasmin, a filtrate of a culture of *Histoplasma capsulatum*, was demonstrated by Christie and Peterson (28) and Palmer (29). These investigators advanced the theory that a mild form of histoplasmosis may result in pulmonary calcification. However, Olsen, Bell, and Emmons (30) were unable to find evidence of a "direct association" between the occurrence of positive histoplasmin skin reactions and pulmonary calcification, although the exact meaning of "direct association" as used in this connection does not seem to have been clearly defined by the investigators.

Geographic variations in the prevalence of pulmonary calcification were reported by a number of investigators, notably by Long and Stearns (31). According to these reports, army inductees from the eastern central region of the United States showed a greater prevalence of pulmonary calcification than those from other areas, and "disseminated miliary calcifications were relatively more frequent in this area." The studies of Palmer (29) and Christie and Peterson (28) have shown that histoplasmin sensitivity was more prevalent in areas with excessive pulmonary calcification, while Zwerling and Palmer (14) reported that, of 15 persons whose chest roentgenograms showed disseminated pulmonary calcification, a total of 14 reacted to histoplasmin. Similarly, of 113 cases described by High, Zwerling, and Furcolow (3), 96.3 per cent of 108 tested reacted to histoplasmin and 10.2 per cent to both tuberculin and histoplasmin. No individual reacted solely to tuberculin.

MATERIAL AND METHODS

All of the 114 individuals included in this study of disseminated pulmonary calcification received one or more clinic examinations. The investigation included a record of identification data, residence since birth, occupation, a history of tuberculosis contact, past and present illness, a physical examination usually limited to the chest, 11 by 14 or 14 by 17 inch P.A. and left lateral or oblique chest films, and tuberculin and histoplasmin skin tests.

Old Tuberculin[4] was used in this study in 1:1,000 and 1:100 dilutions. Earlier in the study, both 1:1,000 and 1:100 dilutions of histoplasmin (H-1 and H-15)[5] were used, but during the last three years only the 1:1,000 dilution was employed, as it was believed to be more specific. Fresh dilutions of tuberculin were made weekly, and of histoplasmin every eight weeks. The dose of tuberculin and histoplasmin was 0.1 ml. given intradermally on the flexor surface of the forearm. The skin tests were given by a small group of clinic physicians and were interpreted by the public health nurse or private physician of the patient

[4] From the Division of Laboratories and Research, New York State Department of Health.

[5] From Dr. Arden Howell, Jr., Public Health Service.

and reported to the clinic office on a special form, with a request that the diameter of the area of induration and of the area of erythema be measured in millimeters on the scale provided on the form. For both skin tests, a reaction was considered positive if induration measuring 5 mm. or more in diameter was found after 48 hours. In order to obtain a rough index of the level of the histoplasmin and tuberculin skin sensitivity of persons in the district, tuberculin and histoplasmin tests were given to a sample group of 305 individuals from the clinic population, excluding cases of disseminated pulmonary calcification. A dilution of 1:1,000 of both tuberculin and histoplasmin was used for the control group.

The cases of disseminated pulmonary calcification presented here were selected according to the criteria and classification suggested by High *et al.* (3). In order to be included in the study, an individual was required to display at least five separate calcific densities scattered throughout at least two-thirds of each lung field. In accordance with High's suggestion, all cases of disseminated pulmonary calcification were divided into two groups, miliary and multiple bilateral calcification. The former were described as "small, round, uniform in size, numerous, and widely and symmetrically scattered throughout each lung field." The latter calcifications were found to be "few in number, often irregular in outline, of varying sizes, and often distributed in an asymmetric pattern." Both groups were further subdivided as to whether or not evidence of calcification was found in the hilar region.

OBSERVATIONS

Geographic distribution: Geographically, the Ray Brook State Tuberculosis Hospital District consists of three parts: a central area, which includes most of the Adirondack State Park, and two relatively level plains bordering on the St. Lawrence River and Lake Champlain. The central area is in large part forest land with scattered villages in the valleys, while the plains adjacent to the St. Lawrence River and Lake Champlain are agricultural districts, with towns, villages, and two small cities.

An analysis of the residential distribution in the present series of 114 persons showing disseminated pulmonary calcification revealed that 106 had lived for at least two-thirds of their lives in either the St. Lawrence or Lake Champlain valleys, 69 in the former and 37 in the latter. One person resided in the Adirondacks. Two of the remaining 7 had lived more than nineteen years in the St. Lawrence valley, one was from Ohio, and the remainder were residents of other areas of New York State. Ninety-four per cent of the persons with such calcifications resided in a valley region and 84 per cent were either farmers, members of farm families, or other equivalents of a typically rural environment. The 18 individuals who gave a history of residence in cities included 12 who had been exposed to dust about the habitat of pigeons, as described below.

Dust exposure: In order to obtain a clue as to possible environmental sources of infection, a history of exposure to the dust of threshing and that about the habitat of pigeons and domestic fowl was ascertained in 78 individuals, of whom 73 (95 per cent) were exposed to one or more of these organic dusts. The exposure history to these dusts was as follows: 10 to threshing, pigeons, and domestic fowl; 20 to threshing and domestic fowl; 4 to pigeons and domestic fowl; 3

to pigeons and threshing; 12 to pigeons alone; 18 to domestic fowl alone; and 6 to threshing alone.

The age of the persons in this study varied from 6 to 79 years; the majority were between the ages of 20 and 50 years. Except for 2 American Indians, all were of the white race. There were 95 males and 19 females.

A study of past illnesses revealed that 42 individuals had never been seriously ill. The 72 patients who had had a previous illness included 40 who gave a history of some severe acute respiratory illness.

Period of observation: The period of observation through the clinics varied from a single visit to sixteen years. Of the 114 individuals, 27 were seen once;

TABLE 1

Symptoms in 114 Cases of Disseminated Pulmonary Calcification

Cough and expectoration	30	
Dyspnea	26	
Chronic fatigue	8	
Wheezing	4	
Chest pain	2	
Total with symptoms		42
Asymptomatic		72

TABLE 2

Physical Examination of the Chest in 114 Cases of Disseminated Pulmonary Calcification

*Diminished increasability of the breath sounds	10	
Rhonchi	8	
Rales	4	
Heart murmurs	2	
Lymphadenopathy (cervical and inguinal)	5	
Total with abnormal physical findings		29
No abnormal physical findings		74
Not examined		11

* Impaired ability to increase the intensity of the inspiratory murmur is believed to be associated with diminished ventilatory function (43).

25 were observed for less than one year; 35, between one and two years; 17, between five and ten years; and 10, between ten and sixteen years. During the period of observation, 72 patients presented no symptoms except those associated with apparently unrelated acute infections. The persistent symptoms observed and their frequency of distribution are given in table 1.

Physical examination: A physical examination was performed in 103 cases and, of these, 74 presented no abnormal physical signs. The physical abnormalities found are shown in table 2.

Roentgenographic examination: On roentgenographic examination there were 49 instances of miliary calcification (figure 1) and 65 instances of multiple bilateral calcification (figure 2). Calcific deposits were found in one or both hila in 59 instances, 21 in the miliary group and 38 in the multiple bilateral group.

The incidence of the two types of calcification and of calcific deposits at the hilum was approximately the same in men and in women.

Other roentgenographic abnormalities associated with disseminated pulmonary

TABLE 3

Familial Occurrence of Disseminated Pulmonary Calcification

FAMILY	SEX	AGE	TYPE OF CALCIFICATION
1	M	10	Miliary
	M	12	Miliary
2	M	23	Multiple bilateral
	M	25	Multiple bilateral
3	M	10	Multiple bilateral
	M	11	Multiple bilateral
	F	12	Multiple bilateral
	F	16	Multiple bilateral
4	M	13	Miliary
	F	16	Miliary
	M*	48	Miliary

* Father—all others siblings.

TABLE 4

Histoplasmin and Tuberculin Skin Tests of 84 Cases of Disseminated Pulmonary Calcification and 305 Controls

SKIN REACTION	DISSEMINATED PULMONARY CALCIFICATION		CONTROLS	
	Number	Per cent	Number	Per cent
H+ T−	37	44.0	29	9.5
H+ T+	42	50.0	14	4.7
H− T+	2	2.4	76	25.1
H− T−	3*	3.6	186	60.7
Total	84	100	305	100
Total H+	79	94.0	43	14.2
Total T+	44**	52.4	90†	29.8

* One individual with equivocal reaction to histoplasmin.

** Old Tuberculin 1:100 in majority.

† Old Tuberculin 1:1,000 in all.

calcification included evidence of pleurisy in 4 and of a previous rib fracture in 2 instances.

A tendency to familial occurrence may be seen in the observation of 11 cases of disseminated pulmonary calcification which belonged to four family units. In three families the siblings affected were distinguished by similar roentgeno-

graphic findings and, in the fourth, the father and two children were found to have similar pulmonary calcification. The distribution among the families by age, sex, and type of calcification is shown in table 3. The accumulation of cases in four families does not, of course, prove that a genetic type of susceptibility may be at work. In order to prove or disprove such a condition, it would be necessary to examine an unselected sample of complete family units exposed to the same environment. This investigation was not feasible.

Histoplasmin and tuberculin tests: In order to obtain an indication of the level of histoplasmin sensitivity in the region, a sample group of the clinic population was tested with histoplasmin and tuberculin. Cases of disseminated pulmonary calcification were excluded. The 305 individuals so tested were about equally divided by sex, and included all age groups. The majority were between the ages of 15 and 44 years. As is shown in table 4, 43 (14.2 per cent) reacted to histoplasmin and 90 (29.8 per cent) to tuberculin.

The results of histoplasmin and tuberculin tests, applied in 84 of the 114 persons with disseminated pulmonary calcification, are given in table 4. Of this group, 79 (94 per cent) reacted to histoplasmin and 44 (52.4 per cent) to tuberculin, while 37 (44 per cent) reacted to histoplasmin alone, 2 (2.4 per cent) to tuberculin alone, and 3 (3.6 per cent) to neither antigen.

Pulmonary Disease Antecedent to Disseminated Pulmonary Calcification

The case histories of 15 persons revealed evidence of a chronic pulmonary disease which had preceded the disseminated pulmonary calcification. In 12 of these patients, it was possible to obtain a story of the mode of onset, early symptoms, and the course of the disease, and it was found in all of the 12 that exposure to excessive concentrations of organic dust immediately preceded the initial symptoms. Persistent, bilateral, widely scattered abnormal shadows were seen in the chest films of all of the 15 cases and these shadows were replaced by disseminated pulmonary calcification during the period of observation.

The clinical picture of the disease may be illustrated by the following examples:

O. A., a married farmer and lifetime resident of the Champlain Valley region, born October 14, 1900, was referred to a chest clinic on November 14, 1938 because of cough and expectoration of four weeks' duration. The past history was noncontributory. In early October 1938 he was engaged in threshing wheat and oats. For a period of ten days he worked in a barn spreading straw which was blown into the mow by the threshing machine. At the end of this time, he suddenly became ill with pain in his arms and legs, anorexia, sweating, chest pain, and a cough which after several days became productive of thick mucoid sputum. An itching rash appeared on the face, neck, wrists, and the lower portion of his legs. Weakness and a loss of 12 pounds in weight occurred. The symptoms gradually subsided over a period of four weeks, except for cough, expectoration, slight fatigue, and occasional chest pain. Physical examinations revealed no abnormalities at the time of the first clinic visit or subsequently. In the initial chest roentgenogram (figure 3) there were a few abnormal shadows, irregular in size and shape, and dispersed throughout both lung fields. Tubercle bacilli were not found in three specimens of sputum examined by the microscopic method after concentration. Cough and expectoration disappeared almost entirely after about six months. Subsequent examinations revealed that the patient was well and working. Per-

sistent symptoms included vague chest pain, frequent acute respiratory infections which were of long duration, wheezing and coryza on exposure to dust of hay and straw, and pain involving the legs, which was more severe following rest and was relieved by exercise. A tuberculin test (1:100) was negative in June 1945 and a histoplasmin test (1:1,000) was positive in April 1947. A review of the 11 chest films taken between November 1938 and May 1948 revealed that a gradual decrease in the size of the widely scattered shadows had occurred, and that by August 1943 evidence of calcification appeared in the central portions of a few of the densities, and eventually in all. By May 1948 the peripheral portion of the shadows had completely disappeared, leaving evidence of a miliary type of calcification in which the individual calcific densities measured 1 to 3 mm. in diameter (figure 4).

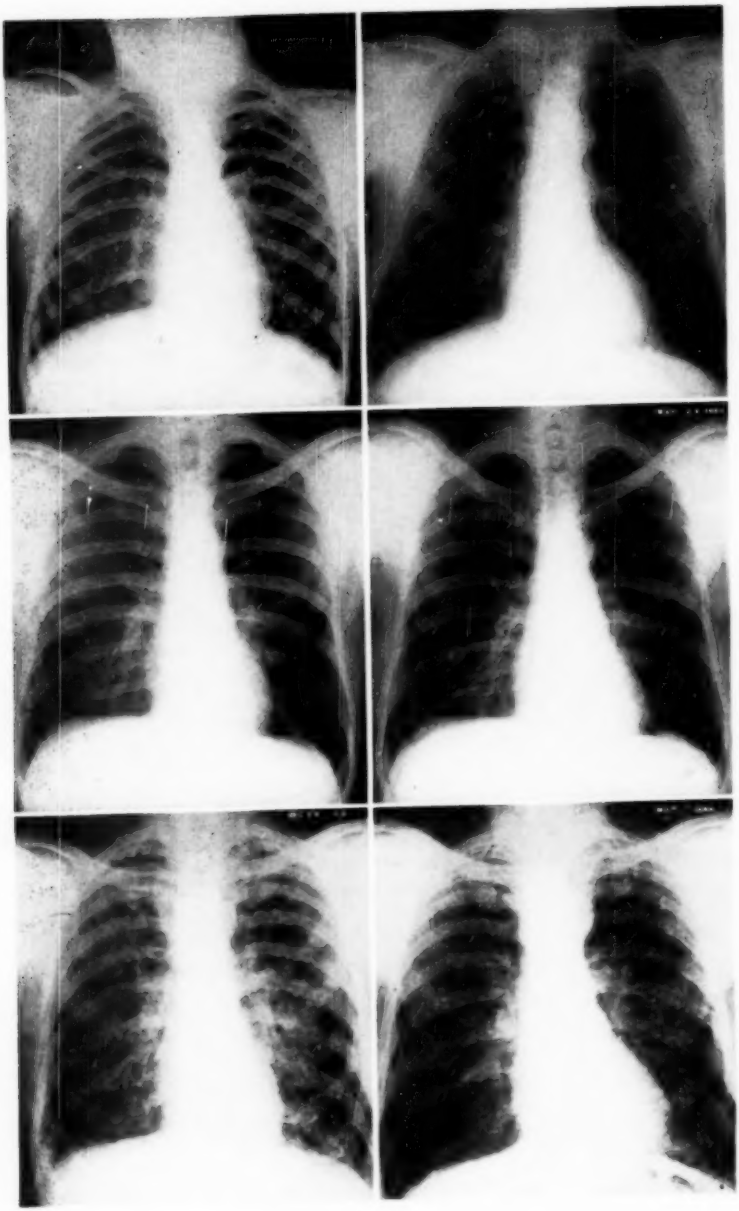
A similar case was that of I. M., a rural mail carrier and lifetime resident of the St. Lawrence Valley region, who was born May 9, 1899, and who became ill in November 1939 following exposure to dust raised while cleaning chicken houses. A chest roentgenogram taken two years prior to this illness was normal. The abnormal shadows in the chest film taken after the onset of the illness were much more numerous than those seen in the roentgenograms of the previously described case. After ten years of observation shadows of less density were still present surrounding a few of the calcific densities. A family study revealed that two of this patient's children had disseminated pulmonary calcification.

Pulmonary Disease Following Exposure to Pigeon Excreta

These observations appeared to be of particular interest, since Nauen and Korns (32) described an epidemic of miliary lung disease which occurred following exposure to dust found about the habitat of pigeons.

Twenty-three men who became ill in November 1938 while engaged in the demolition of an old school building in Plattsburg, New York were studied through the Ray Brook Hospital District Clinic Service. The tower of the school building "was filled with dead pigeons of various sizes and with pigeon droppings to a height of about four feet. Between the roof of the building and the ceiling of the gymnasium was another deposit of manure and dead pigeons about two feet in depth." The removal of the debris produced considerable fine dust, and after seven to fourteen days' exposure to this dust the men became acutely ill. "The illnesses were all remarkably similar and were quite severe in nature. The onset was sudden with chills and fever. In two instances where the temperature was taken, it was recorded as 104°F. and 105°F. An irritating nonproductive cough was present in most cases, and usually ten days to four weeks later this became productive of profuse, thick, gray sputum. Marked weakness and fatigue were prominent features, and about half of the patients complained of anorexia with nausea and vomiting. Headache and chest pain were present in several cases. Most of the illnesses were markedly debilitating, as evidenced by the fact that twelve patients were confined to bed for three to eight weeks and remained away from work for one to five months. There was considerable loss of weight and most patients complained of dyspnea on return to work."

As to the subsequent course of disease in 10 of the cases of Nauen and Korns (32), it may be noted that the early symptoms of the illness subsided about six months after the onset. One patient at that time was free of symptoms and has remained well. A second individual has been asymptomatic except for slight dyspnea on exertion. The remaining individuals have had persistent dyspnea of varying degree, cough, expectoration, and easy fatigability. About one-half of the patients have noted, in addition, intermittent chest pain, occasional night sweats, pain mainly about the joints of the upper and lower extremities, and



FIGS. 1-6

transient wheezing which in one case has been associated with exposure to house dust. Examination of the chest has revealed no abnormal signs in 5 individuals, while in 4 patients there has been evidence of diminished ventilatory function. In 2 individuals it has been possible to elicit rales and rhonchi.

Roentgenographic findings: In view of a marked similarity in the roentgenographic picture of these cases, it appears appropriate to present a composite description. An early film (figure 5) taken one month after the beginning of the illness revealed an enormous number of irregular, relatively large, abnormal shadows scattered throughout both lung fields. In subsequent films the shadows became smaller and more discrete. A slight enlargement of the hilar shadows was noted in 2 cases which disappeared within a period of four months to two years. In 2 instances, evidence of unilateral pleurisy was noted which cleared completely in one case and persisted in the other. Eight to thirty months after the onset of the disease, densities indicating calcification appeared in the central portions of a few of the abnormal shadows. Subsequently, the areas of calcium density increased in number, and gradually the shadows surrounding the evidence of calcification disappeared partially or completely. In the films of one case, calcification was complete in six and a half years but, in the remaining, areas of less dense shadows were still seen around a few of the areas of calcification after ten years of observation. A miliary type of calcification, similar to that shown in figure 6, was noted in all of the 15 cases, and the shadows of the individual areas of calcium density measured 0.5 to 3 mm. in diameter.

Histoplasmin and tuberculin tests: In 13 of the 15 patients, histoplasmin and tuberculin skin tests were performed. All reacted to histoplasmin and 9 to tuberculin. In 9 patients a complement fixation test for histoplasmosis was done, using the yeast phase antigen. Eight were reported as positive with titers varying from 15 to 150. One gave a doubtful reaction, with a titer of 10. Nauen and Korns (32) reported complement fixation tests for ornithosis in 9 of the patients

FIG. 1. (Upper left) The chest roentgenogram of a 12-year-old white male, tuberculin-negative, histoplasmin-positive, illustrating miliary-type disseminated pulmonary calcification with bilateral hilar calcification.

FIG. 2. (Upper right) The chest roentgenogram of a 66-year-old white male, tuberculin-positive, histoplasmin-positive, illustrating multiple bilateral type of disseminated pulmonary calcification.

FIG. 3. (Center left) The chest roentgenogram of a 38-year-old white male farmer. Faint, widely scattered mottled shadows are seen with difficulty throughout both lung fields, most numerous in the lower two-thirds. These developed following exposure to the dust of threshing.

FIG. 4. (Center right) The chest roentgenogram of the same individual as shown in figure 3, 10 years later, showing disseminated pulmonary calcification of the miliary type. This individual was tuberculin-negative, histoplasmin-positive.

FIG. 5. (Lower left) The chest roentgenogram of a 53-year-old white male who developed the evidence of pulmonary disease as illustrated following exposure to dust about the habitat of pigeons.

FIG. 6. (Lower right) The chest roentgenogram of the same individual as shown in figure 5, taken more than 10 years later, showing disseminated pulmonary calcification of the miliary type. Calcification is not entirely complete. Tuberculin and histoplasmin tests were positive.

exposed to pigeon dust. Six gave a negative reaction and the remaining 3 fixed complement in dilutions of 2 to 4. These investigators were able to culture *Moniliae* from the sputum in 12 of the 14 patients from whom sputum specimens were obtained. The significance of this finding is difficult to evaluate, as an unpub-

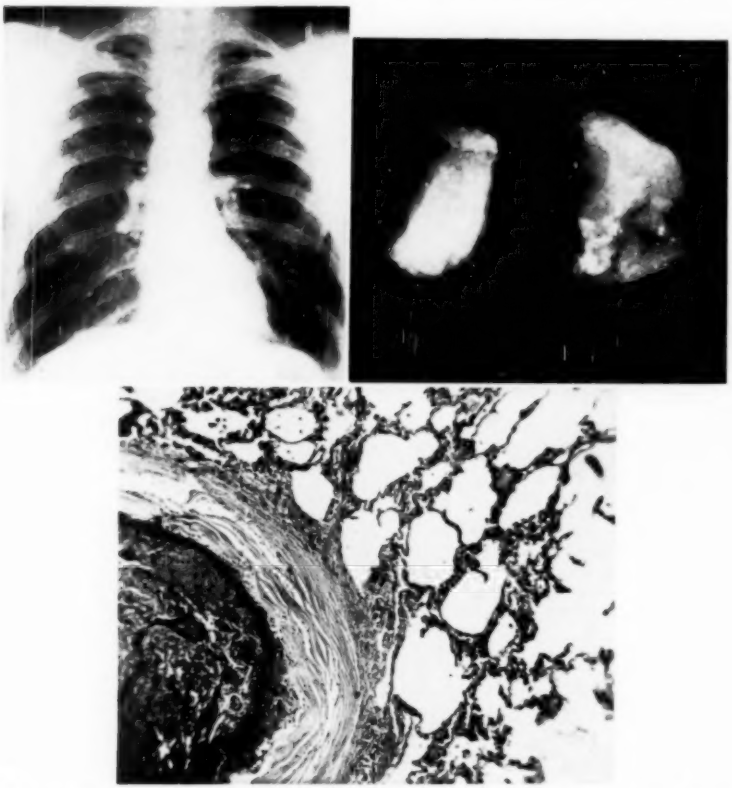


FIG. 7. (Upper left) The chest roentgenogram of a 42-year-old white male taken 3 weeks prior to death. Tuberculin-negative, histoplasmin-positive. Dust exposure is unknown.
FIG. 8. (Upper right) Roentgenogram of excised lung of same individual as in figure 7.
FIG. 9. (Bottom) Photomicrograph of calcified nodule. × 25.

lished study from the Ray Brook State Tuberculosis Hospital, Ray Brook, New York, revealed that one-third of sputum specimens containing tubercle bacilli also showed *Moniliae*.

Morbid Anatomy

In the case of a 42-year-old male laborer included in the study, an autopsy was performed following accidental death. A previous clinic examination about

three weeks before death revealed that the patient was asymptomatic and free of abnormal physical signs except for a few scattered sibilant rhonchi in both lungs. A tuberculin test (1:1,000) was negative, while a histoplasmin test (1:1,000) gave a positive result. Disseminated pulmonary calcification of the multiple bilateral type and bilateral hilar calcification were seen in the chest film which is reproduced in figure 7. A roentgenogram of the excised lungs is seen in figure 8. Death occurred thirty-four hours after the patient had lost consciousness due to a head injury produced by a falling rock. Necropsy revealed that death resulted from a fracture of the skull. All other pathologic changes were confined to the chest. A healed fracture of the right sixth rib posteriorly, pleural adhesions at the apex of the left lung and at the site of the healed fractured rib on the right, and moderate anthracosis in both lungs were noted. Calcified areas were scattered throughout both lungs and were most numerous in the hilar regions.

Sections of the lungs (figure 9) showed two outstanding pathologic changes, namely, an acute lobular pneumonia and focal calcifications, diffuse in distribution. The former change was typical of a terminal pneumonia.

Scattered throughout the lung parenchyma, and with no particular relation to any anatomic structure, many irregularly round foci were observed which showed varying degrees of fibrosis, calcification, and necrosis. The majority of these contained a central core of coarsely granular eosinophilic amorphous material which composed approximately two-thirds of their volume. At the periphery of the necrotic debris was a ring of blue, coarse, granular calcium deposit, 3 to 4 μ in width, which encircled the nodule. Peripheral to the calcium was a dense, encasing ring of hyalinized fibrous tissue, also 3 to 4 μ in width. The dense eosinophilic fibrous tissue strands were disposed in a circular manner, following the circumference of the nodule. There was no inflammatory reaction, either acute or chronic, immediately adjacent to the fibrous tissue band. Apparently normal lung tissue, without evidence of distortion, lay in juxtaposition. No giant cells of any type were encountered within the nodules proper or within their vicinity. Variation in calcification occurred within some of the nodules in that foci of granular calcium deposits occasionally occurred centrally or eccentrically in addition to the peripheral calcified zone described above.

DISCUSSION

The report deals with several cases of a relatively benign chronic pulmonary disease which results in disseminated pulmonary calcification. The etiology of the disease is still obscure. Five similar cases have been reported in the literature. Zwerling and Palmer (14) referred to a case of "active pulmonary disease" in a child whose disease was discovered in a school survey in February 1945. The chest roentgenograms of this case were shown by Furcolow, Mantz, and Lewis (15) in connection with a report of 3 additional cases. Complete studies of the initial case were discussed by Bunnell and Furcolow (16). It is of particular interest that this child was a nonreactor to tuberculin, reacted to histoplasmin skin and complement fixation tests, and that *Histoplasma capsulatum* was cultured from his gastric washings. Furcolow (42), in connection

with a study of the development of calcification in pulmonary disease associated with sensitivity to histoplasmin, has shown that the 4 patients with disseminated pulmonary disease who were previously reported have developed evidence of beginning or complete calcification. *Histoplasma capsulatum* has been recovered by culture from the tonsils of another of these patients. Simpson (17) described one case in which the individual was a nonreactor to tuberculin. In none of the previously reported cases has the onset of the disease been observed clinically. The roentgenographic picture during the period of observation was similar to that described in the present paper.

There is reason to believe that there is some relationship between the disease and organic dust. Disseminated pulmonary calcification has been found by the writers and others (1, 11) to occur more frequently among farmers or rural residents of valley regions, who during the course of their normal occupation might encounter such dusts. The absence of pulmonary disease and disseminated calcification in many farmers and rural residents indicates the significance of some factor other than the dust. The observation of numerous cases of a miliary lung disease immediately following exposure to excessive concentrations of an organic dust would seem to suggest that the dust may serve as a vehicle to convey the causal organisms into the lung. There have been reports of other cases of chronic pulmonary disease in which organic dust was said to act as the vehicle for the inhalation of a fungus. Castellani (33) described tea-tasters' cough, a bronchopulmonary disease affecting tea workers in Ceylon. Fawcett (34) in England and Tornell (35) in Sweden reported a chronic disseminated pulmonary disease occurring among farm laborers who had been exposed to the dust from moldy hay or grain.

Cain (36) recently reviewed four epidemics of an unusual pulmonary disease of unknown etiology, which clinically and roentgenographically closely resembled the early manifestations of the cases reported in the present study. The first outbreak occurred in 5 soldiers at Camp Gruber, Oklahoma, who had been subjected to an extremely high concentration of dust while driving over new roads at the end of a long convoy three days prior to admission to the hospital. Idstrom and Rosenberg (37) reported a pulmonary disease which occurred among 40 men at Camp Crowder, Missouri, in 1944. The disease appeared among men who were engaged in cleaning abandoned houses, barns, and chicken coops. Cain *et al.* (38) described a third epidemic of 26 cases at Camp Gruber, which occurred in 1944. All of the men who became ill had spent some time in an abandoned storm cellar which was reasonably dry, and occupancy by these men may have stirred up dust. Similar conditions were probably operative in a fourth epidemic described by Washburn *et al.* (39) in Arkansas. Twenty-one of 25 persons who had been engaged in a treasure hunt in an old abandoned chalk mine became ill. Washburn referred to a similar epidemic which occurred in Mexico.

Feldman and Sabin (44) observed an outbreak of a miliary lung disease which occurred in 12 men who were exposed to moistened pigeon excreta in an abandoned water tower in Cincinnati. The symptoms, clinical course, and roentgen-

ographic manifestations in the acute phase of the disease were similar to the Plattsburg epidemic. An etiologic diagnosis was not made.

The apparently new disease entity observed in these epidemics differed from the cases presented, in that there had been no pulmonary calcification. However, the cases reviewed by Cain and those of the Cincinnati outbreak were followed for short periods of time, and it is unlikely that sufficient time had elapsed for calcification to occur. Washburn *et al.* (39) and Feldman and Sabin (44) found that skin and serologic tests for histoplasmosis were negative. However, these observations were made in the early stage of the disease when it is not unusual, even in proved cases of histoplasmosis (16, 41), for skin and complement fixation tests to be negative. It is of interest that, although Cain (36) found serologic tests for histoplasmosis to be negative, subsequent studies (45) revealed positive complement fixation tests for histoplasmosis in 18 of 23 of these cases.

The recently reported isolation of *Histoplasma capsulatum* by Emmons (40) from the soil about barns is of interest, particularly in view of the fact that, under laboratory conditions, the organism will grow in the saprophytic phase in soil containing humus. It is possible, therefore, that dust might naturally contain the organism under certain conditions, although it is still uncertain whether dust containing the spores of *Histoplasma capsulatum* is capable of infecting animals or humans.

The previously mentioned isolation of *Histoplasma capsulatum* from 2 cases, the high level of histoplasmin sensitivity in disseminated pulmonary calcification as reported by Zwerling and Palmer (14) and High, *et al.* (3) and confirmed by us, and the positive complement fixation tests for histoplasmosis in those tested suggest that the causal organism of this disease is *Histoplasma capsulatum* or an antigenically related fungus. It is obvious, however, that conclusive proof of a relationship between the given organic dusts and the disease will depend on the demonstration of the specific organism in both the dust and the affected patient.

Studies are in progress in an attempt to demonstrate *Histoplasma capsulatum* in patients with a pulmonary disease associated with a histoplasmin sensitivity and in organic dusts, and will be reported later.

SUMMARY AND CONCLUSION

1. One hundred fourteen cases of disseminated pulmonary calcification, including 15 cases of a preceding chronic pulmonary disease, are described.

2. Ninety-four per cent of these patients resided in a valley region, 84 per cent were farmers or rural residents, and 95 per cent of those questioned gave a history of exposure to an organic dust. There were 95 males and 19 females.

3. Physical signs and symptoms were infrequent in individuals whose disease was in the calcific stage.

4. Multiple cases were found in family groups.

5. Miliary type of calcification was found in 49 individuals, multiple bilateral type in 65, and hilar calcification occurred in 21 of the former, and 39 of the latter, group.

6. Skin sensitivity to histoplasmin was found in 14.2 per cent of a control group and in 94 per cent of the cases of disseminated pulmonary calcification, while skin sensitivity to tuberculin was present in 29.8 per cent of the control group and in 52.4 per cent of the disseminated pulmonary calcification group.

7. The report includes the necropsy findings of a man who had shown evidence of disseminated pulmonary calcification.

8. There is reason to believe that the pulmonary disease resulting in disseminated pulmonary calcification may be an airborne infection due to *Histoplasma capsulatum* or an antigenically related fungus.

SUMARIO Y CONCLUSIONES

Tuberculosis Pulmonar Diseminada: Presentación de 114 Casos con Observaciones de Afección Pulmonar Previa en Quince de Ellos

1. Los 114 casos de calcificación pulmonar difusa aquí descritos comprenden 15 con previa afección pulmonar crónica.

2. Noventa y cuatro por ciento de esos enfermos residían en un valle, 84 por ciento eran labradores o vivían en el campo y 95 por ciento de los interrogados comunicaron antecedentes de exposición a algún polvo orgánico. Del total, 95 eran varones y 19 mujeres.

3. Los signos físicos y síntomas fueron raros en los individuos cuya dolencia estaba en la etapa calcificada.

4. En algunos grupos familares había más de un caso.

5. En 49 individuos encontróse calcificación de forma miliar y en 65 de forma bilateral múltiple, habiendo calcificación hiliar en 21 del primer grupo y 39 del segundo.

6. Descubrióse sensibilidad a la histoplasmina en 14.2 por ciento de un grupo testigo y en 94 por ciento de los casos de calcificación pulmonar difusa, en tanto que existía sensibilidad a la tuberculina en 29.8 por ciento del primer grupo y 52.4 por ciento del segundo.

7. La comunicación comprende los hallazgos autópsicos en un hombre que había revelado signos de calcificación pulmonar diseminada.

8. Hay motivos para creer que la neumopatía que culmina en calcificación pulmonar difusa puede ser una infección aerógena debida al *Histoplasma capsulatum* o a algún hongo antigénicamente afín.

Acknowledgments

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AIR VELOCITY INDEX[1]

A Numerical Expression of the Functionally Effective Portion of Ventilation

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INTRODUCTION

Pulmonary function studies have assumed increasing importance concomitant with the establishment of thoracic surgery as a distinct specialty during the past fifteen years. Many of the newer methods of investigation of the cardiopulmonary system require complex, expensive equipment, and a large medical and technical team. The ventilatory function tests, those dealing with "the mass displacement of air between the outside atmosphere and the interior of the lung" (1), are not only the simplest to perform but are also the most useful to the internist and the thoracic surgeon for objective evaluation of dyspnea, for estimation of surgical risk, and for observation of the effect of various surgical procedures.

The oldest, most widely known, and still most frequently applied of these ventilatory tests is Hutchinson's Vital Capacity (2). Although easily and inexpensively performed, on occasion this test may lead to an erroneous estimation of the patient's ventilatory status inasmuch as vital capacity is a measure of volume only, without consideration of time. The ventilatory insufficiency due to partial obstruction of the pulmonary airways or loss of pulmonary elasticity is due to a slowing of the air stream rather than to a restriction of aerated pulmonary tissue. In such instances, marked dyspnea may be exhibited in the presence of a normal or nearly normal vital capacity.

The maximum breathing capacity, another ventilatory function test, is defined as the largest volume of air that can be moved in and out of the chest voluntarily during a given period of time (3). The time element here is included, and this test has proved to be an excellent measure of ventilatory function which can be closely related to subjective dyspnea. The maximum breathing capacity, however, gives no indication as to whether ventilatory insufficiency is due to obstruction to the flow of expired air or to a decrease of the total quantity of aerated pulmonary tissue available.

Absolute measurement of the speed of air flow requires the use of a pneumotachograph, a device which records air velocity directly, instantaneously, and linearly (4, 5). Nevertheless, a comparison of vital capacity and maximum breathing capacity does give some indication as to whether ventilatory insufficiency is due to obstruction or decrease of the amount of available parenchymal lung tissue. Thus, if the reduction of maximum breathing capacity is greater than that of the vital capacity, some obstruction to the flow of air must exist. This is most

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frequently seen in "obstructive" pulmonary emphysema, bronchial asthma, and anatomic bronchostenosis. Such patients, if given sufficient time to expel one single maximal breath, will show a vital capacity which may be nearly normal. If the maximal volume of expired air is measured in relation to time, however, as by the maximum breathing capacity test, a severe reduction in total volume will be noted. If both vital capacity and maximum breathing capacity are normal or reduced to an equal extent, a comparison of the two will indicate absence of obstructive factors.

In the past, direct comparison of vital capacity and maximum breathing capacity has yielded disappointing results (6, 7). It has been shown that little relationship existed between the two in certain types of pulmonary disease, while in others there was better agreement. The explanation of these findings lies in the fact that maximum breathing capacity in liters per minute was compared to vital capacity in liters. Individual variations of these values with age, sex, height, and weight are so great that deviations due to disease are overshadowed. Adequate formulas for the calculation of normal predicted vital capacity and maximum breathing capacity for any given age, sex, height, and body surface have been reported (1). If these two values are expressed as per cent of the predicted and then compared, a very definite pattern emerges. We have expressed this relationship by the ratio

$$\frac{\text{per cent of predicted maximum breathing capacity}}{\text{per cent of predicted vital capacity}}.$$

The resulting figure was named *Air Velocity Index*, since it is related to the velocity of expired air rather than to absolute ventilatory function. For example, if the vital capacity is 80 per cent of predicted and the maximum breathing capacity 40 per cent of predicted, the index is 40/80 or 0.5; if the maximum breathing capacity is reduced less than the vital capacity, the index will be larger than 1.0. Theoretically a normal Air Velocity Index should be 100 per cent/100 per cent, or 1.0.

The present report deals with experiences with the Air Velocity Index in 435 patients studied on 476 occasions.

METHODS

Maximum breathing capacity: Expired air was collected for periods of 30 seconds with a high velocity respiratory valve, a three-way gas cock, and a Douglas bag (8). The volume of gas was measured with a compensated Tissot spirometer, the volume was corrected for 37°C., and reported in liters per minute. The regression formula for calculation of predicted values was $(86.5 - (0.522 \times \text{age in years})) \times \text{m}^2$ B.S. for males and $(71.3 - (0.474 \times \text{age in years})) \times \text{m}^2$ B.S. for females, where m^2 B.S. is the body surface in square meters (1).

Vital capacity: Expired air was collected and measured with a 6-liter spirometer. The volume was corrected to 37°C., and reported in liters. The regression formula for calculation of predicted values was $(27.63 - (0.112 \times \text{age in years})) \times$ height in cm. for males and $(21.8 - (0.101 \times \text{age in years})) \times$ height in cm. for females (1).

Both the maximum breathing capacity and the vital capacity were obtained with the patient in the sitting position. All tests were repeated at least three times and more often if consecutive results of increasing magnitude were obtained. Only the best effort was re-

ported. Tests were interrupted by ten- to fifteen-minute rest periods. Patients were urged to maximal effort during the performance of both tests.

OBSERVATIONS

A summary of the results is presented in table 1. Scatter diagrams of figures 1, 2, and 3 are so constructed that each point represents one patient with the per cent of predicted vital capacity as the abscissa and the per cent of predicted maximum breathing capacity as the ordinate. The position of each point represents the Air Velocity Index. All points which fall below a line drawn at 45° from the intersection of the coordinates represent an Air Velocity Index of less than 1.0, and all those above this line an index over 1.0.

TABLE 1

The Air Velocity Index of Normal Volunteers, in Pulmonary and Bronchial Disease and after Thoracic Surgical Procedures

DISEASE	NUMBER OF CASES	NUMBER OF STUDIES	M.B.C. MEAN PER CENT PREDICTED	V.C. MEAN PER CENT PREDICTED	AIR VELOCITY INDEX	
					Mean	Range
Normal volunteers	23	23	113	106	1.07	1.00 to 1.36
Effective loss of aerated lung tissue						
Advanced tuberculosis	112	112	90	80	1.19	0.90 to 2.00
Empyema and hydrothorax	16	16	76	55	1.39	1.06 to 2.22
Pneumothorax	17	17	81	56	1.44	1.07 to 1.92
Thoracoplasty	94	94	70	54	1.29	0.79 to 1.87
Lobectomy	20	20	79	58	1.37	1.04 to 2.08
Pneumonectomy	25	25	72	49	1.46	0.86 to 1.74
Disease of the pulmonary airways						
Tuberculosis, air "trapping"	37	37	57	67	0.85	0.63 to 1.54
Tuberculous bronchostenosis	19	19	59	69	0.86	0.73 to 1.02
Carcinoma, partial occlusion	8	8	65	98	0.66	0.47 to 1.13
Pulmonary emphysema	28	51	42	68	0.62	0.32 to 1.00
Bronchial asthma	36	54	29	69	0.42	0.19 to 0.88

Normal volunteers: Twenty-three normal volunteers were recruited from the medical and nursing staff of the hospital. The maximum breathing capacities of the group ranged from 95 to 130 per cent of predicted, with a mean of 113; and their vital capacities from 85 to 120 per cent of predicted, with a mean of 106. The AVI for the group ranged from 1.00 to 1.36, with a mean of 1.07 (table 1, figure 1).

Pulmonary resection: Forty-five patients were studied, following pneumonectomy and lobectomy (table 1, figure 2). Both groups showed a considerable reduction of ventilatory function, more marked in the pneumonectomy group. Mean vital capacity was 58 per cent of predicted for lobectomy and 49 per cent for pneumonectomy. The same figures for the maximum breathing capacity were

79 and 72 per cent, respectively. The mean AVI was significantly elevated in both groups, 1.46 after pneumonectomy and 1.37 after lobectomy. All patients were studied six months after operation. None of the pneumonectomy patients showed laboratory evidence of emphysema, though only 12 of the 25 had had a postoperative thoracoplasty. A number of postpneumonectomy patients with evidence of emphysema were seen at the laboratory. These were usually in the

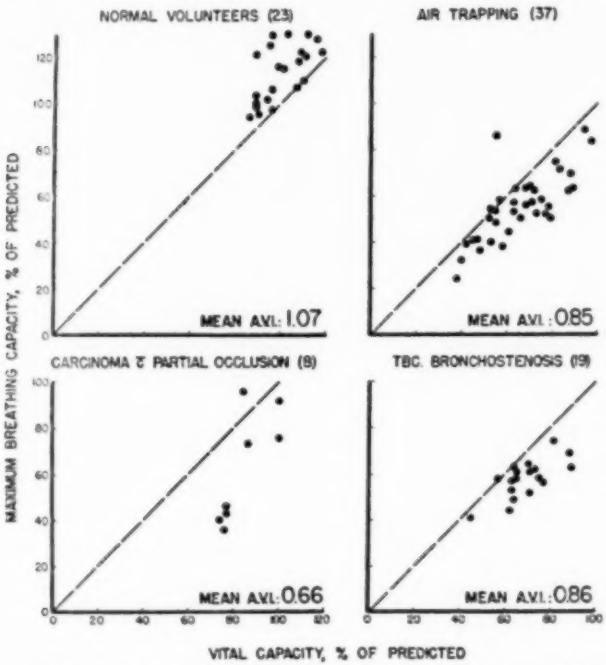

FIG. 1. Relationship of vital capacity and maximum breathing capacity expressed by the Air Velocity Index (AVI) in normal volunteers and in patients with bronchostenosis due to tuberculosis and bronchogenic carcinoma.

older age group and were observed from one to three years after operation. They were included in the emphysema group below.

Collapse therapy: Ninety-four patients with thoracoplasty and 17 patients with pneumothorax were studied six months after induction of collapse. Ventilatory insufficiency was evident in both groups, and there was a greater reduction of vital capacity than of maximum breathing capacity in both groups. This discrepancy was more marked in the pneumothorax cases, with a mean AVI of 1.44, than in the thoracoplasty group, with a mean AVI of 1.29 (table 1, figure 2.) The effect of the two types of collapse on pulmonary function cannot be compared

since the preoperative function of the pneumothorax group was normal or nearly so, while most thoracoplasty patients showed considerable pulmonary insufficiency even before operation.

Reduction of aerated pulmonary parenchymal tissue due to disease: Two types of loss of aerated lung tissue were studied: advanced pulmonary tuberculosis in 112 patients, and empyema or hydrothorax in 16 patients (table 1, figure 3). Reduction of ventilatory function, present in both, was more severe in the empyema group. The AVI was slightly elevated in the advanced tuberculosis group with a mean of 1.19, and greatly elevated in the empyema and hydrothorax group, with

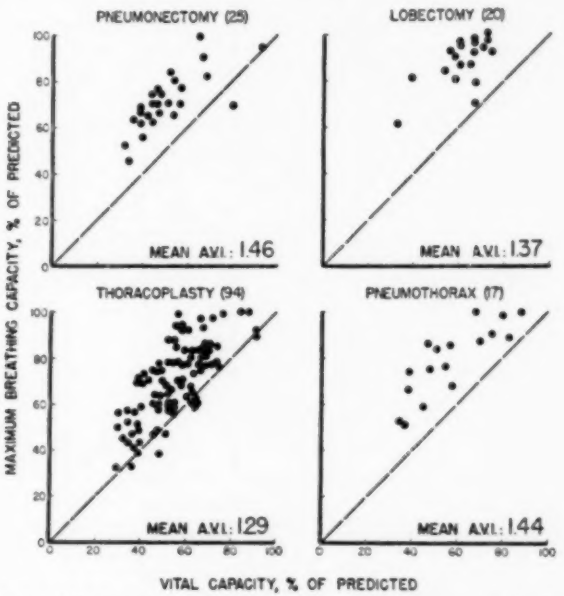

FIG. 2. Relationship of vital capacity and maximum breathing capacity expressed by the Air Velocity Index (AVI) of patients after pulmonary collapse therapy and after resection.

a mean of 1.39. The latter group of patients can be compared with the pneumonectomy group since 13 of the 16 patients had total collapse of one lung and none retained more than 20 per cent of their total function on the affected side, as demonstrated by bronchospirometry.

Bronchial asthma: Thirty-six patients with bronchial asthma were studied on 54 occasions. When first seen at the laboratory none of these patients was dyspneic, though many of them showed clinical signs of mild asthma. Severe asthmatic attacks were occasionally induced by intravenous administration of histamine or methacholine. An occasional patient developed dyspnea after performance of the maximum breathing capacity, and many had severe attacks induced by topical

anesthesia prior to bronchospirometry. The mean values, therefore, represent a considerable range of severity of bronchospasm (10). The mean predicted maximum breathing capacity of 29 per cent was much smaller than that observed in emphysema, thoracoplasty, empyema, or even pneumonectomy; while the mean vital capacity of 69 per cent of predicted was greater than that of any of the other groups. The mean AVI of 0.42 was the lowest encountered in any group. There was no index above 0.88 and some were as low as 0.19. The reduction of

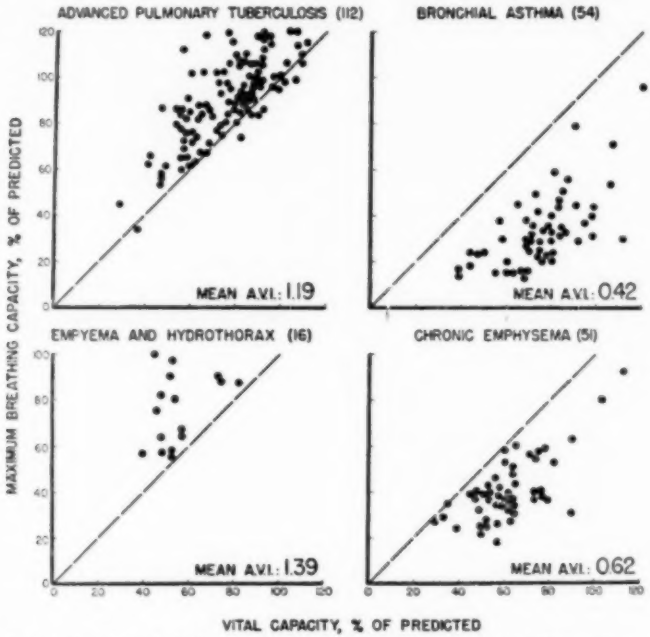

FIG. 3. Relationship of vital capacity and maximum breathing capacity expressed by the Air Velocity Index (AVI) of patients with loss of available pulmonary parenchymal tissue because of tuberculosis or empyema, and of patients with diffuse bronchial obstruction and loss of pulmonary elasticity because of chronic emphysema and bronchial asthma.

AVI correlated very well with the severity of the asthma, though even patients completely free of symptoms showed a decreased AVI (table 2). Some of these gave a history of bronchial asthma while others denied even this, and latent asthma was only detected when bronchodilator aerosols produced a marked increase of maximum breathing capacity and a restoration of the AVI to normal (10).

Chronic emphysema: All 28 patients with chronic emphysema had severe symptoms. Further evidence of emphysema was obtained by residual air studies in most and by arterial blood studies in some. The emphysema was associated with

pulmonary tuberculosis in 7; with a history of bronchial asthma in 4; and with previous pneumonectomy for bronchiectasis, lung abscess, and bronchogenic carcinoma in 3. Sixteen patients were studied before and after treatment with pneumoperitoneum (11). Ventilatory insufficiency was expressed by a reduction of mean maximum breathing capacity to 42 per cent of predicted. With the exception of the asthma group, this was the lowest encountered. The mean vital capacity of 68 per cent of predicted was slightly lower than that of the asthma patients (table 1, figure 3). The mean AVI was 0.62.

Tracheobronchial obstruction: There was evidence of anatomic bronchial obstruction in 64 patients. Partial obstruction of a major bronchus was visualized at the time of bronchoscopy in 27 patients. This was due to bronchogenic carcinoma in 7 patients, to a bronchial adenoma in one, and to tuberculosis in 19 patients. In 37 patients there was no evidence of obstruction at the time of bronchoscopy but localized "trapping" of air on rapid expiration, seen on fluoroscopy, gave evidence that such obstruction existed in smaller divisions of the bronchi. All patients in this group showed evidence of ventilatory insufficiency. This was more apparent when assessed by estimation of the maximum breathing capacity, than by measurement of the vital capacity. The mean AVI was reduced to 0.86 in the tuberculous stenosis group, and to 0.85 in the "air trapping" group. Patients with partial occlusion of the bronchus due to carcinoma and adenoma showed a greater reduction of air flow velocity as expressed by an index of 0.66 (table 1, figure 1). Several patients were seen with complete obstruction of a major bronchus due to carcinoma. These did not show this pattern but showed rather an increase above normal of the AVI and segmental or lobar atelectasis on roentgenographic examination of the chest.

COMMENT

The subjects in the above studies can be divided into two groups, those with an Air Velocity Index greater than 1.0 and those with less than 1.0 (table 1).

Obstruction of the expiratory air stream due to spasm or anatomic reduction of the bronchial lumen invariably resulted in an index of less than 1.0. The decreased AVI of pulmonary emphysema may be due both to loss of pulmonary elasticity and to bronchiolar spasm and narrowing. The index was smallest in bronchial asthma (table 1) and the reduction appeared to be proportional to the severity of symptoms (table 2). A good correlation existed between the AVI and those patients in whom "trapping" of air had been recorded previously from fluoroscopic findings.

The AVI was increased in all patients who were suffering from a loss of aerated pulmonary parenchymal tissue. The increase varied from 1.19 for patients with pulmonary tuberculosis to 1.46 for patients with pneumonectomy. The elevation of the index appeared to be roughly related to the extent of loss of aerating surface. It was smaller with lobectomy than with pneumonectomy and larger with total empyema than with thoracoplasty. A correlation was shown to exist between the unilateral loss of function as demonstrated by bronchospirometry and the increase of AVI.

Reduction of the speed of the expiratory air stream in the group with an AVI less than 1.0 is easily understood and is readily attributed to the physiologic abnormalities present. The cause for an increase of the Air Velocity Index in the second group may not be immediately apparent. The development of an elevated index becomes clear when individual patients are followed with weekly or monthly function studies following extensive resection or thoracoplasty (9). In such patients a large and equally extensive reduction of both vital capacity and maximum breathing capacity is apparent immediately following operation. Resection or collapse has irreversibly reduced the vital capacity which is now, as before, limited by the extent of thoracic and diaphragmatic motion. As postoperative pain subsides, function studies show an initial small increase of vital capacity, with little or no further improvement after that. The maximum breathing capacity continues to increase over the course of four to six months and after pneumonectomy or extensive thoracoplasty may even reach preoperative levels (9). Patients whose total aerating surface has been suddenly reduced by surgical interference learn in the course of time to breathe more efficiently, more rapidly, and with greater coordination. Under stress they are therefore able to overcome some of their handicap. This is very noticeable when such patients are observed during a maximum breathing capacity test. Respirations are faster and frequently more regular than those of normal individuals, and the effort does not appear to tire them as much. An additional factor may be that onset of respiratory alkalosis due to the voluntary overbreathing is more delayed than in normal individuals since their total exchange of air is relatively small. A comparison of the mean per cent of predicted maximum breathing capacities will further emphasize this point (table 1). While the mean value for normal persons was 113 per cent, that for pneumonectomy or total empyema was not one-half of normal, or 57 per cent, but rather 72 and 76 per cent, respectively, despite the presence of considerable disease in the remaining lung in many of the patients. The same is not true for the vital capacity. Here the mean per cent of predicted was 49 for pneumonectomy and 55 for total empyema, or roughly one-half of the 106 per cent found in normal persons. The Air Velocity Index, therefore, slowly increases after operation to values considerably greater than normal. The same, but to a lesser extent, is true after lobectomy and selective thoracoplasty and the same evolution of a high AVI holds true for advanced pulmonary tuberculosis. Extrapleural pneumothorax, which does not cause significant loss of maximum breathing capacity, gives rise to a small increase of the AVI (12, 13).

The regression formulas used for calculation of predicted figures were obtained from the study of "pulmonary normal" patients of a hospital population (1). As a result the figures for predicted normal performance, arrived at by these formulas, tend to be low (9). Furthermore, maximum breathing capacities for the calculation of the formula were obtained by rebreathing air from a closed recording spirometer (1). Although resistance of such a system can be reduced to a minimum by omission of soda lime and flutter valves, by use of large tubing and a large spirometer bell, inertia of the bell cannot be eliminated. The maximum breathing capacities calculated from such spirometer tracings are there-

fore lower than those obtained by the high speed valve and Douglas-bag method used by us (8, 9). The Air Velocity Index for our group of normal volunteers is slightly larger than 1.0 because the regression formula for the maximum breath-

TABLE 2

Air Velocity Index Calculated from Ventilatory Studies Reported in the Literature

AUTHOR	DISEASE	CLASSIFICATION	NUMBER OF CASES	REPORTED		CALCULATED AVI
				M.B.C. Mean per cent	V.C. Mean per cent	
Baldwin, Cournand, and Richards (15)	Emphysema	Arterial oxygen above 92% after exercise	25	43	72	0.60
		Arterial oxygen below 92%, CO_2 tension below 48 mm. Hg.	19	37	69	0.54
		Arterial oxygen below 92%, CO_2 tension above 48 mm. Hg.	15	29	59	0.49
		With cor pulmonale	9	28	68	0.41
Motley, Lang, and Gordon (16)	Emphysema	Residual air less than 25% of total lung capacity	14	73.9	93.5	0.79
		Residual air 25 to 35% of total lung capacity	23	63.7	80.9	0.79
		Residual air 35 to 45% of total lung capacity	30	44.9	64.2	0.70
		Residual air 45 to 55% of total lung capacity	18	33.0	56.7	0.58
		Residual air over 55% of total lung capacity	15	26.0	44.9	0.58
Gaensler and Carter (11)	Emphysema	Before pneumoperitoneum	13	33.2	59.2	0.56
		After pneumoperitoneum	13	43.0	69.5	0.62
Gaensler (10)	Bronchial asthma	Asymptomatic	9	41.2	82.5	0.50
		Signs of bronchospasm, no dyspnea	17	27.8	73.2	0.38
		Severe asthma, dyspnea at rest	8	18.3	67.8	0.27
Baldwin, Cournand, and Richards (17)	Fibrosis	With ventilatory insufficiency	25	75	75	1.00
		With alveolo-respiratory insufficiency	14	83	46	1.80

ing capacity results in a relatively larger per cent of predicted values than the formula for the vital capacity (table 1).

The cooperation of patients in the performance of maximum breathing capacity is usually excellent. Variation of results from one attempt to another and from one day to another is smaller than for any other voluntary test of ventila-

tion (14). In the present series there was only one patient who was unable to perform the test satisfactorily because of excessive secretions. Variations of vital capacity are somewhat larger, and there is an occasional patient who cannot understand the required maximal inspiration and expiration. Nevertheless, variation here is smaller and agreement with other pulmonary function studies better than a number of other widely used tests of respiratory function (14).

A few investigators have recently reported large series of function studies using the same formulas for prediction of normal values that have been used in the present study. The results of their studies and our calculation of the AVI are summarized in table 2. Two series of patients with pulmonary emphysema are recorded. Baldwin and associates, reviewing 122 cases, graded the severity of emphysema according to arterial oxygen hemoglobin saturation and carbon dioxide tension (15). In their four groups of emphysema there was remarkable agreement between the blood gas studies and the AVI. Motley and associates, in a study of 100 coal miners with dyspnea, graded emphysema according to per cent of total pulmonary capacity occupied by residual air (16). Here too the AVI was greatly reduced, and there was good correlation between the AVI and severity of emphysema, but it was not as close as that with arterial blood studies. We have studied patients with severe emphysema before and after treatment with pneumoperitoneum (11). Such treatment caused not only a reduction of residual air and an increase of both maximum breathing capacity and vital capacity but also some increase of a greatly reduced AVI. A recent study made in this laboratory of 34 patients with bronchial asthma showed a very good correlation of severity of symptoms and AVI, although even asymptomatic asthmatic patients showed a remarkable reduction of the AVI to 0.50 (10). Patients with pulmonary fibrosis uncomplicated by emphysema, reported by Baldwin and associates (17), showed no reduction of AVI; on the contrary, those without ventilatory insufficiency showed a compensatory increase similar to our group of patients with loss of aerated pulmonary lung tissue (table 2).

SUMMARY

1. Ventilatory studies were performed in 435 patients on 476 occasions.

2. A definite relationship was shown to exist between the maximum breathing capacity and the vital capacity. It was best expressed by the formula

$$\frac{\text{per cent of predicted maximum breathing capacity}}{\text{per cent of predicted vital capacity}}.$$

This relationship was called Air Velocity Index since it was shown to be related to the speed of the expiratory air speed and unrelated to actual ventilatory insufficiency.

3. The Air Velocity Index was increased in patients with loss of aerated pulmonary parenchymal tissue due to disease or collapse therapy. The increase was proportional to the loss of tissue. The mean index was 1.07 for 23 normal volunteers, 1.19 for 112 patients with advanced pulmonary tuberculosis, 1.29 for 94 patients with thoracoplasty, 1.39 for 16 patients with total empyema, 1.37

for 20 patients with lobectomy, 1.46 for 25 patients with pneumonectomy, and 1.44 for 17 patients with pneumothorax.

4. The Air Velocity Index was decreased in patients with bronchial obstruction and loss of pulmonary elasticity. It was 0.86 for 19 patients with tuberculous bronchostenosis, 0.85 for 37 patients in whom "trapping" of air was visualized on fluoroscopy, 0.66 for 8 patients with partial occlusion of major bronchi due to carcinoma, 0.62 for 28 patients with pulmonary emphysema, and 0.42 for 36 patients with bronchial asthma.

5. The Air Velocity Index was calculated from the data of a number of studies of pulmonary function reported in the literature. There was agreement with results obtained in the present study.

SUMARIO

El Indice de Aero-Velocidad: Expresión Numérica de la Porción Funcionalmente Efectiva de la Ventilación

1. En 435 enfermos ejecutáronse estudios de la ventilación en 476 ocasiones.

2. Observóse una relación bien definida entre la capacidad respiratoria máxima y la capacidad vital, que queda mejor expresada en la fórmula.

$$\frac{\text{Por ciento de la capacidad respiratoria máxima predicha}}{\text{por ciento de la capacidad vital predicha}}.$$

Esta relación ha sido denominada Indice de Aero-Velocidad por haberse demostrado que está enlazada con la celeridad del aire expirado y no guarda relación con la insuficiencia ventilatoria presente.

3. El Indice de Aero-Velocidad aumentó en los enfermos que habían perdido, por virtud de enfermedad o colapsoterapia, tejido parenquimopulmonar aireado, siendo el aumento proporcional a la pérdida de tejido. El Indice medio fué: 1.07 en 23 voluntarios normales, 1.19 en 112 enfermos con tuberculosis pulmonar avanzada, 1.29 en 94 pacientes con toracoplastias, 1.39 en 16 enfermos con empiema total, 1.37 en 20 enfermos lobectomizados, 1.46 en 25 neumonectomizados y 1.44 en 17 enfermos con neumotórax.

4. El Indice de Aero-Velocidad disminuyó en los enfermos con oclusión bronquial y pérdida de elasticidad pulmonar, representando: 0.86 en 19 enfermos con broncoestenosis tuberculosa, 0.85 en 37 en que la roentgenoscopia permitió visualizar atrape de materias, 0.66 en 8 con oclusión partial de bronquios mayores debida a carcinoma, 0.62 en 28 con enfisema pulmonar y 0.42 en 3 con asma bronquial.

5. El Indice de Aero-Velocidad fué calculado para varios estudios de la función contenidos en la literatura, concordando con los resultados obtenidos en el estudio actual.

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FURTHER OBSERVATIONS ON THE PATHOLOGICAL PHYSIOLOGY OF CHRONIC PULMONARY GRANULOMATOSIS ASSOCIATED WITH BERYLLIUM WORKERS[1,2]

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INTRODUCTION

A preliminary report (1) on the causes of dyspnea in 6 patients with chronic pulmonary granulomatosis associated with beryllium compounds confirmed the findings of Wright *et al.* (2). The essence of the pulmonary disturbances was considered to be widening of the alveolar-arterial gradient for oxygen. This was due to alterations in the structure and volumes of the lungs, which impaired distribution and diffusion of respiratory gases. Hyperventilation occurred with exertion. Maximum breathing capacity was found to be quite variable. Proportionately greater reduction in complemental air than increase in *volume* of residual air made the structural changes more closely resemble pulmonary fibrosis than emphysema. Diminished exercise tolerance was marked in patients with pulmonary heart disease resulting from increased resistance to blood flow. In most instances polycythemia was not found, and the possible toxic effect of beryllium compounds was considered. It was not known whether the metabolic disturbances were due to chronic hypoxemia alone or in association with unrecognized tissue poisoning of enzyme systems.

There has been no opportunity for further studies on these patients. One person (A. B.) died within a year but, in the absence of post-mortem examination, the exact relationship of granulomatosis to the cause of death was not obtained. Two others (J. J. and W. R.) recently died of their disease, and 3 have shown some improvement. Three additional male patients have been studied. Each had a definite history of industrial exposure to beryllium compounds, which is presumed to be causally related to the pulmonary disability. In addition to the same cardio-respiratory observations made on the former patients, quantitative estimates of physical fitness, further analyses of the pulmonary diffusion characteristics, and an investigation of the effects of continuous oxygen therapy have been made.

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[2] This work is part of a cooperative study of beryllium toxicology in human subjects carried out by the Department of Medicine of the University of Rochester School of Medicine and Dentistry under the direction of Dr. William S. McCann in collaboration with the Division of Medical Services of the Atomic Energy Project, and aided by grants from the Hochstetter Fund, University of Rochester School of Medicine and Dentistry.

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[4] With the technical assistance of S. J. Vernarelli.

METHODS

The methods employed for the study of these 3 patients were the same as those previously reported (1). In addition, Marie Krogh's carbon-monoxide method of estimating pulmonary permeability was used on one patient (3), utilizing an iodine pentoxide method for the determination of carbon monoxide in the air samples (4). The principle of Krogh's method used to estimate alveolar membrane permeability is expressed in the following formula:

$$K = \frac{\log A - \log B}{0.4343(t)}$$

Where K = permeability of lungs in ml. of CO per minute that would diffuse into the blood if the lungs were filled with pure CO, and blood pCO was zero

Where t = time for exposure and absorption of CO in minutes

Where A = initial alveolar concentration of carbon monoxide

Where B = final alveolar concentration of carbon monoxide after elapsed time (t) from sampling A

0.4343 = $\log_{10} e$

Approximately 75 ml. of 96 per cent pure commercial carbon monoxide were mixed with 6.0 liters of air in a suitable spirometer; the patient was asked to exhale rapidly and completely, then inhale this gas mixture quickly, expire about one-half the volume rapidly for initial CO gas sample A, and then hold the breath for about six seconds before expiring the remaining volume of the gas mixture.Both the time of exposure and the volume of gas mixture were recorded. Similar studies were made on normal controls for comparison.

From these data the diffusion constant for CO at the observed breathing level (near the mid-capacity level) can be calculated as follows:

$$D_{co} = \frac{(K)\ (\text{observed volume} + \text{residual air volume} - \text{dead space})}{\text{B-47}}$$

Since the absorption coefficients of CO, CO_2, and O_2 are known, and the diffusion constant for another gas, such as O_2, varies directly with the absorption coefficient and inversely with square root of the molecular weight, the other diffusion constants become:

$$D_{co_2} = \frac{D_{co}(0.568)(\sqrt{28})}{(0.0184)(\sqrt{44})} = 24.6D_{co}$$

$$D_{o_2} = \frac{D_{co}(0.0242)(\sqrt{28})}{0.0184(\sqrt{32})} = 1.23D_{co}$$

Physical fitness for moderate exercise has been estimated from the least variable characteristics of cardio-respiratory performance (5). These factors are the duration of exercise, mean exercise respiratory efficiency, and recovery pulse.

The proportions of effective alveolar ventilation, nonfunctioning alveolar ventilation, and dead-space ventilation have been calculated (by the Bohr equation from observed expired air and mid-capacity (terminal expired air) pO_2 values (1), and the ideal alveolar pO_2 based upon the R.Q. and arterial pCO_2 values (6). Similarly, the proportion of effective alveolar perfusion has been estimated by assuming a normal oxygen gradient; hence, at least 95 per cent saturation of pulmonary venous blood. The ideal alveolar pO_2 has been used as reference point for the partitioning of the observed mid-capacity to arterial pO_2 gradient into ventilation and perfusion components. The former represents the effects of the distribution factor, whereas the latter represents the alterations due to venous admixture, when one assumes there may be no diffusion factor.

The metabolic effects of continuous oxygen therapy were made by Doctor Waterhouse

on 2 beryllium patients and one patient with pulmonary cystic disease and emphysema who served as a control (7).

CASE REPORTS

G. G. (No. 285349, 65.4 kg., 1.71 m^2 surface area) was a 48-year-old white male who enjoyed excellent health until April 1945. During one month's exposure to beryllium compounds in the form of dust, he developed a skin rash within the first ten days, and subsequently experienced paroxysms of coughing, sneezing, and vomiting. Roentgenographic examination of the chest was reported to show the pulmonary infiltrations of acute pneumonitis. Some degree of exertional dyspnea was present at this time but, after three months' convalescence, he was able to work in a shipyard for two years, until November 1947. He then had a recurrence of respiratory symptoms as well as fatigue, irritability, anorexia, and loss of 47 pounds in body weight. A "positive" chest roentgenogram in March 1948 was responsible for his stopping work. Physical examination on admission in September 1948 revealed a well-developed middle-aged man with some evidence of recent weight loss. There was no respiratory distress or cyanosis. The blood pressure was 120 systolic and 80 diastolic in mm. of mercury, and the vital signs were normal. The chest expanded well; the lung fields were clear to auscultation. The heart size by percussion was at the upper limits of normal, the rhythm was regular, and the second pulmonic sound was slightly accentuated, whereas the first sound at the apex was split. There were varicose veins in the legs. Roentgenographic examination of the chest (figure 1) revealed hazy, granular infiltrations in the lung fields bilaterally, and some prominence of the pulmonary conus in the cardiac silhouette. The diaphragmatic excursions were limited to 2 cm. by fluoroscopy. The maximum breathing capacity was normal; determinations of lung volumes showed a reduction of vital capacity and total pulmonary capacity (table 1). The breathing pattern was regular. Breath-holding time was 21.5 seconds. Electrocardiographic study revealed no abnormalities other than low voltage of the QRS complex, and inverted T wave in aV_L lead which was compatible with vertical position of the heart. The ballistocardiogram showed apparently low cardiac output. The venous pressure was 7.0 cm. of water, and circulation times were 8.5 seconds arm to lung and 14 seconds arm to mouth. Level walking caused slight dyspnea and fatigue, together with hyperventilation and diminished respiratory efficiency (figure 2). The resting mid-capacity-arterial oxygen gradient was increased (table 2), largely due to the perfusion component (ideal alveolar pO_2 − arterial pO_2). As a consequence there was hypoxemia (table 3), but there was no alteration of CO_2 content or hemoglobin concentration (hematocrit 47 per cent). By means of cardiac catheterization, normal values for cardiac output and A-V oxygen difference were observed. The right ventricular pressure was found to rise above the normal range as a result of transient leg exercises.

After convalescence from contact dermatitis and acute pneumonitis allegedly following industrial exposure to beryllium compounds, this patient was well for two years and then suffered a relapse with respiratory and metabolic disturbances compatible with chronic pulmonary granulomatosis. Functional studies showed reduced complemental air volume, increased oxygen gradient, hypoxemia and hyperventilation, as well as incipient pulmonary hypertension on exertion.

L. H. (No. 291142, 55.4 kg., 1.64 m^2 surface area) was a 26-year-old white male who was employed in a clerical position in a fluorescent-lamp factory between 1940 and 1943. During July 1947, while in the Army, he developed a nonproductive cough and had some changes in his chest roentgenogram. By the following February he experienced fatigue, excessive coughing followed by vomiting, and later noticed anorexia and exertional dyspnea. On examination in January 1949 he appeared asthenic. There was slight cyanosis and clubbing of the nails, but no respiratory distress at rest. The chest expanded adequately, but there were signs of emphysema on percussion and auscultation. The heart was not enlarged,

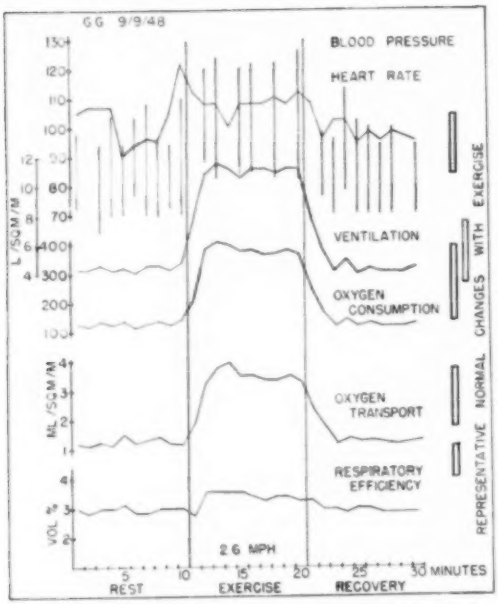


FIG. 1. (Upper) Chest roentgenogram of patient G. G.

FIG. 2. (Lower) Exercise tolerance test of patient G. G. Note the low blood pressure and labile heart rate, especially during rest, and hyperventilation together with diminished respiratory efficiency (volumes per cent of oxygen absorbed from air, as determined from the expired air pO_2 values) during exercise.

and the only abnormality was the persistent finding of premature contractions. The blood pressure was 104 systolic and 74 diastolic in mm. of mercury. Chest fluoroscopy showed a diffuse, hazy, granular lung field bilaterally, and the cardiac silhouette was unremarkable except for a long narrow shape. In the roentgenogram (figure 3) there were innumerable discrete small nodular shadows throughout the lungs, in addition to the features of emphysema. Determinations of lung volumes showed a striking reduction in vital capacity and total capacity, together with an increase in the residual air volume (table 1). The breathing

TABLE 1

Pulmonary Capacities in Liters at BTPS

PATIENT	MAXIMUM BREATHING CAPACITY OBSERVED*	VITAL CAPACITY*	COMPLEMENTARY AIR	MID-CAPACITY	RESIDUAL AIR	TOTAL CAPACITY*	PER CENT OF OBSERVED TOTAL CAPACITY		DEAD SPACE
							MID-CAPACITY	RESIDUAL AIR	
	L. m²/min.								
G. G.	72.3 (117)	2.81 (75)	2.03	2.24	1.25	4.06 (85)	55	31	.134
L. H.	63.6 (87)	2.09 (76)	2.14	2.33	1.97	4.06 (76)	57	48	.189
B. W.	82.5 (132)	1.08 (27)	1.08	1.53	0.77	1.85 (46)	83	42	.145
L. T.	40.5 (55.6)	1.76 (39)	1.65	4.12	3.33	5.09 (86)	81	65	.353

* Per cent of predicted capacity for age, sex, and height.

TABLE 2

Resting Oxygen Gradients and Respiratory Efficiency

PATIENT	pO_2, MM. Hg				GRADIENTS, MM. Hg			RESPIRATORY EFFICIENCY
	Inspired	Mid-capacity*	Ideal Alveolar	Arterial	Observed	Ventilation Perfusion Components		
								volume per 100 cc.
G. G.	148	113	102	81	32	11	21	3.52
L. H.	143	115	105	68	47	10	37	2.58
B. W.	146	129	115	65	64	14	50	2.39
L. T.	146	126	121	73	53	5	48	2.47
Representative normal values	146	115	104	95	20	11	9	4.04

* The pO_2 of terminal expired air, or end-tidal air, representing the pO_2 of mixed alveolar air at the mid-capacity breathing level.

pattern was interrupted by frequent deep, sighing inspirations, and there was a Christie effect indicative of diminished pulmonary elasticity. The maximum breathing capacity was slightly reduced. The mid-capacity-arterial oxygen gradient was considerably increased (table 2), and unsaturation of the arterial blood (table 3) was present.

The hematocrit was 47 per cent, and the hemoglobin was normal. The resting venous pressure was 9.8 cm. of water, and arm-to-lung and arm-to-mouth circulation times were eight and sixteen seconds, respectively. The electrocardiogram showed vertical position of the heart and multiple auricular and ventricular premature beats. The ballistocardiogram indicated a normal cardiac output, and the patterns were normal except for moderate degree of respiratory variation. Exercise tolerance tests (figure 4) performed at 1.73 m.p.h.

level walking caused no symptomatic distress during ten minutes' exertion. There was about 1.5 per cent decline in arterial oxygen saturation (by the oximeter) despite moderate

TABLE 3

Observations during Cardiac Catheterization

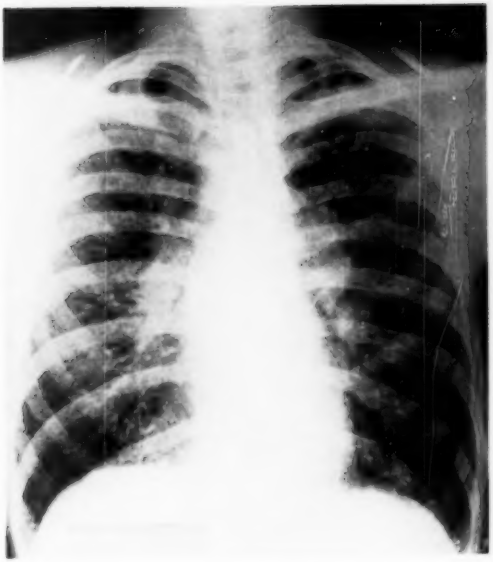
	REPRESENTATIVE NORMAL VALUES	PATIENTS				
		L. T.	G. G.	L. H.	B. W.	B. W.*
Barometric pressure	747	747	744	731	752	743
Respiratory rate	14	12	18	28	25	27
R.Q.	0.85	1.14	0.82	1.12	1.05	0.79
Dead space ventilation, liters per minute, BTPS	1.5	4.24	3.55	6.43	6.56	5.93
Tracheobronchial tree, per cent	22	30	33	44	27	38
Nonfunctioning alveolar, per cent	13	11	16	9	22	24
Effective alveolar ventilation, liters per minute	4.7	8.31	3.73	5.49	6.86	3.69
Per cent of total ventilation	66	59	51	46	51	38
Arterial blood pCO_2, mm. Hg.	38	29	38	42	30	39
pO_2, mm. Hg.	95	73	81	68	65	69
Oxygen content, volume per 100 cc.	19	17.7	17.9	16.2	16.8	14.7
Carbon dioxide content, volume per 100 cc.	47	—	46.7	44.0	41.4	48.6
Oxygen saturation, per cent	95	91.5	90	86	87	89
Hemoglobin concentration, gm. per 100 cc.	15	14.6	15.0	14.0	14.4	12.3
A-V oxygen difference, ml. per liter	50	64	50	42	40	50
Cardiac output, liters per minute	5.0	4.33	4.04	6.00	6.55	4.58
Heart rate	80	70	104	90	109	111
		(R. ventr.)	(R. ventr.)			
Mean pulmonary arterial pressure, mm. Hg.	13	9.2	11.6	23.5	14	16
Effective pulmonary perfusion, per cent of cardiac output**	95	91	83	72	72	84
Effective alveolar $\frac{\text{ventilation}}{\text{perfusion}}$ ratio	.99	2.11†	0.99	1.27	1.45	0.96

* Breathing room air temporarily, on ninth day of oxygen therapy.

** Assuming 95 per cent saturation of blood leaving capillaries of functioning alveoli.

† Acute hyperventilation from anxiety at time of direct Fick determination.

hyperventilation. The respiratory efficiency was abnormally low during both rest and exercise. No circulatory or electrocardiographic abnormalities were observed during the exercise, and the premature beats continued at the same relative frequency. Another exercise



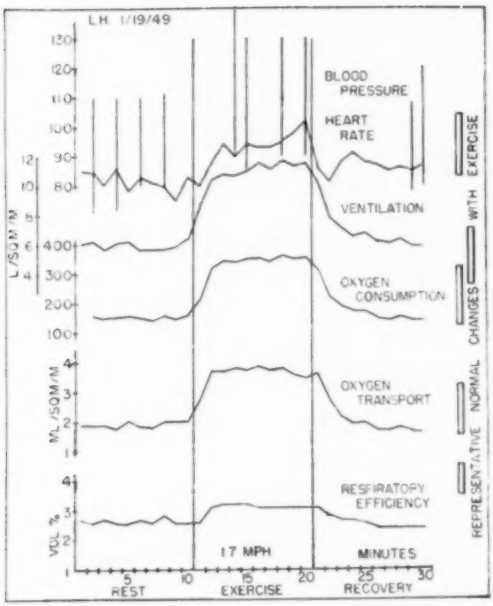


FIG. 3. (Upper) Chest roentgenogram of patient L. H.

FIG. 4. (Lower) Exercise tolerance test of patient L. H. During the exercise an appreciable degree of hyperventilation and diminished respiratory efficiency were observed.

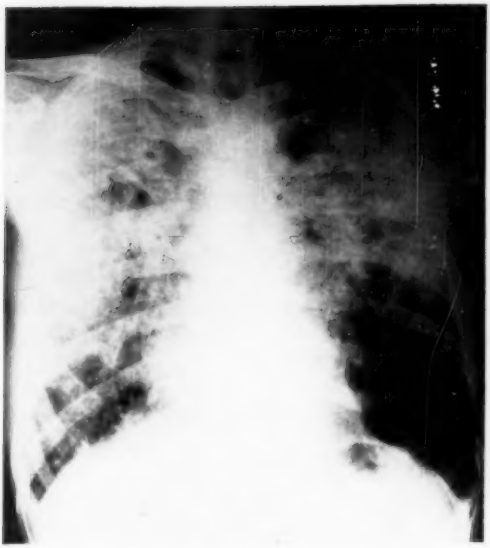
test at 5 per cent incline also caused no symptomatic distress, and similar lack of dyspnea was noted with level walking at 2.6 m.p.h. for ten minutes. Cardiac catheterization revealed a normal cardiac output and A-V oxygen difference (table 2). Also there was evidence of pulmonary hypertension, and leg exercises further increased the pulmonary arterial pressure.

This patient presented more pulmonary involvement than the former patient, yet had an almost normal ventilatory capacity despite the altered lung volumes. The mid-capacity-arterial oxygen gradient was considerably increased. Although there was hypoxemia and pulmonary hypertension, the heart was not enlarged by roentgenographic examination. Hyperventilation accompanied exertion.

B. W. (No. 283928, 41.8 kg., 1.40 m^2 surface area) was a 31-year-old white male who was in good health until December 1946. He was employed in a fluorescent-lamp factory in 1941, was in the Army between 1942 and 1946, after which he returned to his former job. He began to lose appetite and weight, tired easily, and felt listless. By January 1947 he noticed a hacking cough and dyspnea on exertion; roentgenographic examination of the chest was considered compatible with beryllium granulomatosis. He was hospitalized, treated with streptomycin, and developed allergic reactions with fever and generalized "swelling" of the tissues. Breathing exercises seemed to alleviate the dyspnea somewhat. He had noticed dyspnea even at rest on some occasions, and had been unable to gain any weight. Ingestion of food, or exertion, had caused palpitations for some time. On examination in March 1949 the patient appeared chronically ill, asthenic, with moderate respiratory distress and evidence of weight loss. There was slight cyanosis, but no clubbing. The chest showed an increased A-P diameter, and accessory muscles were being used even for the resting level of breathing. Chest expansion was equal and adequate; the lungs were hyper-resonant to percussion; and auscultation revealed emphysematous breath sounds with a prolonged expiratory phase. No rales were present. The heart was not enlarged; the blood pressure was 95 systolic and 60 diastolic in mm. of mercury. The abdomen was scaphoid.

The chest roentgenogram (figure 5) showed a combination of basilar emphysema, and diffuse bilateral confluent soft shadows intermingled with relatively clear cystic areas in the upper lung fields. The cardiac shadow was elongated. On fluoroscopy the diaphragmatic excursion was found restricted to 1 cm., and prominence of the pulmonary conus together with an unusually clear aortic window in LAO view were observed. The maximum breathing capacity was greater than the average normal capacity (table 1). In contrast, the vital capacity and the total capacity were greatly reduced (table 1). Although the residual air volume was 79 per cent of the predicted volume, it was 42 per cent of the observed total capacity. The resting venous pressure was increased to 15.5 cm. of water, and rose another centimeter with pressure over the right upper quadrant of the abdomen (table 3). Electrocardiographic study showed sinus tachycardia of 116 per minute, and vertical position of the heart with low voltage in lead one and CF_5. The ballistocardiogram showed fairly normal complexes with some respiratory variations. The hemoglobin concentration was normal. There was definite hypoxemia associated with a greatly widened mid-capacity-arterial oxygen gradient (table 2). In addition, hypocapnia secondary to hyperventilation was observed (table 3). This patient was able to walk for ten minutes at 1.73 m.p.h. without any symptomatic distress (figure 6). The heart rate and blood pressure rose to 140 per minute and 126 systolic and 94 diastolic in mm. of mercury, but the oxygen debt was only 8.3 per cent. He exhibited marked hyperventilation (with considerable reduction of respiratory efficiency) even in excess of the metabolic demand, since the average R.Q. of expired air during the exercise was 1.03.

Cardiac catheterization was performed; the right auricular pressure was within normal limits, although the right ventricular systolic pressure slightly exceeded the normal range. The cardiac output was 6.55 liters per minute, with an A-V oxygen difference of 4.0 volume



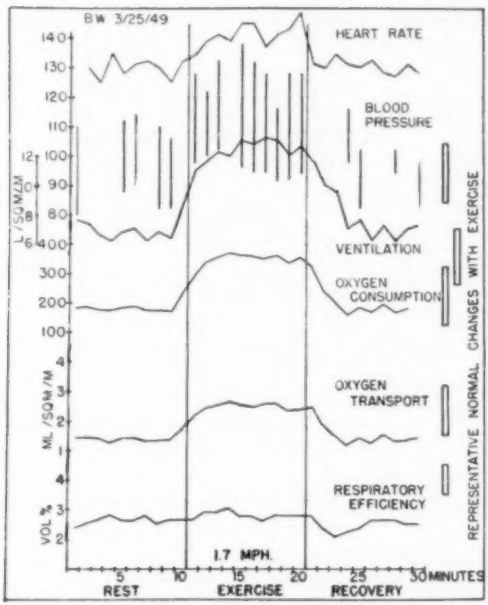


FIG. 5 (Upper) Chest roentgenogram of patient B. W. Note the contrasting shadows in the upper lobes and the translucency of the emphysematous lower lobes.

FIG. 6. (Lower) Exercise tolerance test of patient B. W. Rather marked sinus tachycardia, hyperventilation, and depressed respiratory efficiency were noted throughout the three periods of observation. Since the resting oxygen consumption was also elevated, these changes were probably in part related to anxiety.

per 100 cc. The stroke volume during rest was 60 ml. Breathing oxygen by a mask promptly increased the arterial oxygen saturation 5.5 percentage points within a minute (oximeter). For purposes of metabolic investigation, this patient was treated with continuous oxygen therapy for a period of ten days (see below).

It is of interest to note that this patient first developed clinical symptoms of pulmonary granulomatosis associated with beryllium compounds five years after exposure. Moreover, he also presented the usual features of variable degrees of respiratory distress, exertional dyspnea, and malnutrition. The chest roentgenogram confirmed the physical signs of emphysema and revealed considerable confluent nodular shadows in the upper lung fields. Despite marked reduction of complementary air volume, ventilatory capacity was not impaired. This was all the more remarkable since fluoroscopic examination revealed limited diaphragmatic excursions. In addition to hypoxemia, this patient exhibited hypocapnia from over-breathing in excess of the metabolic needs of the tissues.

L. T. (No. 285656, 66 kg., 1.84 m^2 surface area) was a 26-year-old white male who had had asthma and exertional dyspnea since childhood. He had signs of marked emphysema and expiratory wheezing. Roentgenographic examination of the chest revealed a large cyst in the right lower lobe, and fluoroscopy showed paradoxical motion of the diaphragm. The residual air volume was 3.7 liters, 325 per cent of the predicted value, or 53 per cent of the observed total capacity. He required over twenty seconds to perform a vital capacity, and the spirogram showed a Christie effect of the mid-capacity baseline. Although the venous pressure was normal, the circulation times were prolonged to 23 and 27 seconds for arm to lung and arm to mouth, respectively. Electrocardiogram showed evidence of auricular hypertrophy. The arterial oxygen saturation was reduced, the cardiac output was normal, and no pulmonary hypertension was present (table 2). Five months after lobectomy (RML and RLL) the vital capacity was diminished further. Then the arterial oxygen saturation was 89 per cent, with a pCO_2 of 38 mm. of mercury. After suitable control observations, he was given continuous oxygen therapy for several days to ascertain if correction of the chronic hypoxemia would influence his nitrogen metabolism. Although the arterial oxygen saturation rose to 97.4 per cent, with pO_2 of 173 mm., there was no significant change in his metabolic status. After cessation of oxygen therapy, he felt better and was less dyspneic; his residual air volume had decreased 0.48 liter, with a slight increase in the vital capacity; and these changes persisted until he was re-examined two months later. The circulation times became normal after the oxygen period.

GENERAL OBSERVATIONS

Physiologic investigations of the causes of dyspnea in 3 additional patients with chronic beryllium granulomatosis revealed the following factors in common with the patients originally studied: (*1*) reduced complemental and total pulmonary capacities (table 1); (*2*) increased oxygen gradient of the lungs (table 2); (*3*) hypoxemia (table 3); and (*4*) exertional hyperventilation (figures 2, 4, and 6). There were, of course, individual variations in the magnitudes of each of these common features.

Division of the total ventilation into the effective alveolar, nonfunctioning alveolar, and dead space ventilation of the tracheobronchial tree demonstrated that conspicuous increments in nonfunctioning alveolar ventilation had occurred in some patients, whereas tachypnea was responsible for much of the overbreathing in other patients (table 3). As a corollary of these changes, respiratory

efficiency (cc. of oxygen absorbed from each 100 cc. of air ventilated) diminished. The inability to attain an adequate complemental volume of air on inspiration contributed further to the conscious awareness of dyspnea and respiratory embarrassment. Inevitably intrapulmonary mixing was impaired and hypoxemia ensued. If anxiety further stimulated the ventilatory effort, hypocapnia could occur during the experimental observations, e.g., in patients L. T. and B. W.

Although the resting pulmonary arterial pressure was not regulary increased in these patients, L. H. presented evidence of pulmonary hypertension. Abnormally high cardiac output values during rest (where the effects of anxiety could be excluded) were not observed. In all 3 patients the estimated pulmonary

TABLE 4

Estimation of Physical Fitness

	PATIENT	RATE	AVERAGE EXERCISE RESPIRATORY EFFICIENCY	TOTAL HEART BEATS FIRST 3 MINUTES OF RECOVERY	INDEX
		m.p.h.	*volume per 100 cc.*		
1.	A. B.;	2.60	4.04	359	11.25
2.	M. E. T.	2.60	2.99	351	8.52
3.	M. C.	2.60	3.64	261	13.9
4.	M. H. C.	2.60	3.07	446	7.13
5.	J. J.	1.73	2.56	385	6.6
6.	G. G.	2.60	3.35	305	10.9
7.	L. H.	1.73	3.06	255	12.0
8.	B. W.	1.73	2.81	394	7.14
9.	L. T.	2.60	3.96	358	11.0
Mean normal		2.6	5.03 (4.2 to 5.9)	265	19.1

The values for the first 5 patients listed were taken from the admission data on exercise studies previously reported (1).

Normal values for these work loads range between 12 and 26 for the fitness index. All patients walked for ten minutes.

capillary perfusion was reduced from 71 to 83 per cent of the cardiac output (normally at least 93 per cent (6)). Acute transient exposures to high, inspired oxygen tensions failed to raise the arterial pO_2 above 69 mm. in patient L. H. and 182 mm. in patient B. W. No evidence of congenital intracardiac shunts was found. Hence, there were rather marked variations in alveolar perfusion as well as in alveolar ventilation in these patients.

A comprehensive evaluation of cardio-respiratory performance during standardized exercise has been derived from the physical fitness index (table 4) (5). The results obtained from these 3 patients, as well as from 5 ambulatory patients previously studied, showed that only M. C. gave a score which fell within the normal range of 12 to 26. The lowest value, 6.6, was recorded for J. J. who was the most disabled of the ambulatory patients. Diminished respiratory efficiency

was present in all patients, and tachycardia further contributed to the diminished fitness score in some of the patients.

Observations on pulmonary gas exchange in patient B. W.: There was no significant difference in the pulmonary permeability, estimated by means of carbon monoxide, in patient B. W. (5.0 ± 2.0 ml., 10 observations) as compared with normal subjects (7.0 ± 1.8 ml., 17 observations, $p > 5.0$). There were significant differences in the diffusion constants, however, since the mean for B. W. (12.1 ± 4.2) was reduced from the normal range (28.5 ± 6.7, $p < .006$). Of the two factors responsible for impaired diffusion, permeability, and lung volumes, the

TABLE 5

Estimations of Alveolar-arterial Pressure Gradients for Oxygen in Patient B. W.

	3/25	5/27*	6/15	6/16
Inspired pO_2, mm. Hg	146	145	146	105
Mid-capacity pO_2, mm. Hg.†	129	119	120	91
Ideal alveolar pO_2, mm. Hg	115	94	107	53
Arterial pO_2, mm. Hg	65	69	62	51
Observed gradient (MCpO_2—Art. pO_2)	64	50	58	40
Ventilation component (MCpO_2—Ideal pO_2)	14	25	13	38
Perfusion component (Ideal pO_2—Art. pO_2)	50	25	45	2
Arterial pCO_2, mm. Hg	30	39	36	39

* At the time of this observation the patient had been breathing oxygen continuously for 9 days, and this supplemental oxygen therapy was interrupted long enough to permit satisfactory measurements to be made while breathing room air. Hence these data represent the acute response to hypoxia.

The ideal alveolar pO_2 has been estimated from:

$$\text{insp. } pO_2 + \frac{(\text{art. } pCO_2)\ (\text{insp. } O_2\%)\ (1 - \text{R.Q.})}{100\ (\text{R.Q.})} - \frac{\text{art. } pCO_2}{\text{R.Q.}}$$

† The pO_2 of terminal expired air, or end-tidal air, representing the pO_2 of mixed alveolar air at the mid-capacity breathing level.

second was the more important in this patient. Hence, there was a reduction in the number of normally functioning alveoli.

Acute exposures to hypoxia diminished the observed mid-capacity-mixed arterial pO_2 gradient (table 5). With this change in the total observed gradient there was an increase in the ventilation component as well as a reduction in the perfusion component. The greater change occurred with the more severe hypoxic stimulus. In each instance the arterial pCO_2 increased to 39 mm., but this change in itself was not considered sufficient to account for the entire variations in the two components of the observed gradient for oxygen.

In order to investigate the effects of continuous oxygen therapy on metabolic processes which might in part be deranged because of chronic hypoxemia, oxygen

was administered continuously to patient B. W. for ten days. The exact inspired oxygen concentration was not determined, and undoubtedly varied with the effectiveness of the nasal catheter during the daytime or the oxygen tent used during the night. The arterial oxygen saturation was found to be between 92.6 and 98.0 per cent within the first thirty hours of this regimen. The oxygen was well tolerated, as the effort of breathing diminished. Progressive alterations of lung volumes occurred until the vital capacity diminished from 1.74 to 1.22 liters as the residual air volume increased from 1.06 to 2.93 liters. Trapping of air from bronchospasm seemed unlikely as the observed values for the tracheobronchial tree dead space were found to increase somewhat. Concomitantly the arterial oxygen tension and saturation were observed to fall toward the control values prior to the oxygen program. On the ninth day of continuous oxygen therapy, cardiac catheterization was repeated; lower values for cardiac output, stroke volume, effective alveolar ventilation, and respiratory quotient were obtained (table 3). However, these more nearly normal values probably reflected a decrease in the effects of anxiety together with greater ease of breathing. Retention of electrolytes and gain in weight occurred during oxygen therapy (8). The venous pressure was not increased. Following the cessation of oxygen therapy the patient experienced a severe relapse in symptoms characterized by intense dyspnea, anorexia, nausea, weakness, depression, and irritability which precluded any further physiological studies. After several days he felt improved, and it was found that his lung volumes, ventilatory effort, arterial blood gas composition, and exercise tolerance were quite similar to the initial values.

Similar untoward after-effects of the same type of continuous oxygen therapy were not observed in the emphysematous patient, L. T., who served as a control. Furthermore, there were slight alterations in the lung volumes, but in the opposite direction, which persisted up to two months and were accompanied by subjective improvement and greater exercise tolerance.

DISCUSSION

The functional alterations common to most of the patients with chronic beryllium granulomatosis have been summarized above under general observations. These changes are nonspecific, since they may be demonstrated in patients with pulmonary insufficiency attributed to other etiologic factors. Because of the severity of the hypoxemia and no marked increase generally in the volume of residual air in the lungs, these patients might be considered in the second group of pulmonary fibroses described by Baldwin *et al.* (9).

The capacity for moderate work is obviously greatly impaired in these patients. The physical fitness index appears to reflect quantitatively the degree of impairment. Other studies have indicated that the fitness index varies inversely with the observed oxygen gradient of the lungs, and directly with the partial pressures of oxygen in the blood, especially the calculated mean capillary pO_2 during rest (10). Hence, the abnormally high oxygen gradients and hypoxemia are major factors contributing to the disability encountered in these patients.

When appropriate indications are present, it is customary to administer oxygen therapy continuously, as long as the need for it exists. Whereas this may be an uneventful procedure for acutely ill patients, experience has shown that continuous oxygen therapy may create a vicious problem for the patient suffering chronically from hypoxemia. Ordinarily "oxygen poisoning" is not considered to occur in cyanotic patients, but the unexpected changes in lung volumes and gradual reduction of arterial oxygen saturation, together with the severe withdrawal symptoms in patient B. W. after discontinuing oxygen therapy for ten days, raises the possibility of "oxygen toxicity." During oxygen therapy, dyspnea was relieved as the ventilatory effort was diminished. The effective alveolar ventilation was markedly reduced without significant change in dead space and nonfunctioning alveolar ventilation, and there was an apparent recovery from

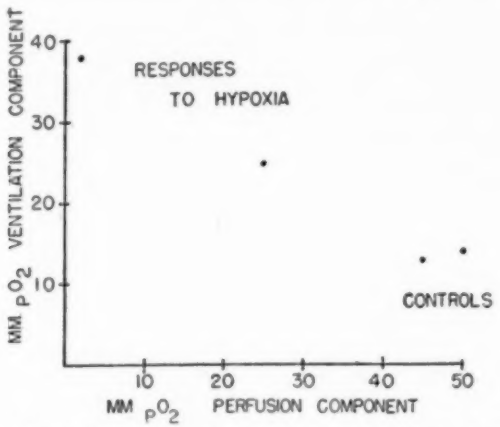


FIG. 7. Effects of acute hypoxic stimuli on ventilation and perfusion components of mid-capacity to mixed arterial oxygen gradient in B. W. See text for discussion.

hypocapnia. Concomitantly the residual air volume of the lungs was nearly tripled. These changes suggested some adaptation to a higher inspired oxygen tension which necessitated the reverse acclimatization when oxygen therapy was discontinued. The initial adaptation to oxygen therapy was not achieved within the first day. Accompanying these changes was retention of salt and water and, although the body weight transiently increased, there was no rise in venous pressure. The respiratory effects of adaptation to oxygen have been interpreted as the combination of relative hypoventilation with opportunity for CO_2 retention and pulmonary hyperemia. Although some alteration in the diaphragms might have occurred, we were unable to demonstrate it in this patient. It is noteworthy that the emphysematous patient, who served as a control subject for the metabolic investigation of oxygen therapy, exhibited a minimal, but prolonged, symptomatic and objective improvement immediately after a period of continuous oxygen therapy.

In view of these considerations, it is prudent to caution against the use of *continuously* administered oxygen therapy for patients with chronic intractable hypoxemia. Appreciable symptomatic benefit, without as yet objective evidence of untoward effects, accrues from the intermittent use of oxygen for short periods of twenty to thirty minutes several times daily. Not only is such a regimen more economical, but less likely to be "toxic."

SUMMARY

Three more cases of chronic pulmonary granulomatosis associated with beryllium compounds have been studied with reference to pulmonary and circulatory functional capacity. Despite obvious variations in clinical patterns of disease between patients, certain nonspecific general trends of functional disturbance appear common to most of these patients. They are restricted complemental air volume, increased mid-capacity-arterial oxygen gradient, hypoxemia, and hyperventilation on exertion. The complexity of factors contributing to the widened oxygen gradient is discussed. A general quantitative estimate of disability in relation to moderate exercise is expressed in terms of the physical fitness index. Untoward responses to continuous oxygen therapy are recorded.

SUMARIO

Nuevas Observaciones Relativas a la Fisiología Patológica de la Granulomatosis Pulmonar Crónica en los Trabajadores con Berilio

Tres casos más de granulomatosis pulmonar crónica asociada con los compuestos del berilio han sido estudiados con respecto a la capacidad funcional del pulmón y la circulación. A pesar de manifiestas variaciones en los patrones clínicos de la enfermedad en distintos enfermos, ciertas tendencias generales anespecíficas de los trastornos funcionales parecen existir en la mayor parte de estos pacientes, a saber: limitación del volumen de aire complementario, aumento de la capacidad media, pendiente del oxígeno arterial, hipoxemia e hiperventilación con el ejercicio. Discútese la complejidad de los factores que afectan la ampliación de la pendiente de oxígeno. Un cálculo cuantitativo general de la incapacidad en relación con el ejercicio moderado es expresado en términos del índice de aptitud física. Menciónanse respuestas adversas a la oxigenoterapia continua.

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THE PATHOGENESIS OF CHRONIC SUBSTANTIAL (HYPERTROPHIC) EMPHYSEMA[1]

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Elucidation of the pathogenesis of chronic diseases always has been difficult. This is particularly true for those instances where, in the absence of a specific injurious agent, disturbance of function precedes irreparable structural alterations and leads to advanced and crippling morphologic changes over a long period of time. The resulting picture is a kind of morphologic epilogue of disturbed function, often of many years' duration. It is like a document of historical events, revealing some facts but withholding essential information of the exact nature and sequence of occurrences in the past.

In this study, an attempt is made to coordinate a few facts based mainly on roentgenographic observation, with the hope of adding a missing link to our knowledge of the mechanics of emphysema.

DEFINITIONS

The term "pulmonary emphysema," literally inflation of the lung, is used to designate several different pathologic conditions, and there exists a confusing multitude of related and qualifying terms.

(*1*) *Acute vesicular emphysema, volumen pulmonum auctum*, reversible functional emphysema or effort lung. This type of emphysema is encountered with acute bronchitis and bronchiolitis, especially in children; in bronchial and cardiac asthma; and in persons who die from suffocation or drowning. The pulmonary overdistention, due in some instances to bronchial obstruction and in others to increased inspiratory effort, may be similar to that which occurs in chronic emphysema and may cause the latter when persistent over a long period of time.

(*2*) *Senile emphysema*, chronic, atrophic, vesicular emphysema or small-lunged emphysema is believed to be a part of the general involutionary process occurring with age. It is not associated with mechanical strain. In its pure form the chest is small and the lung is also small; the interalveolar septa are thinned and often partially resorbed, giving rise to confluence of adjacent air sacs. Revival of the old theory that deformity and rigidity of the chest cause emphysema has recently lead to the concept that degenerative changes of the thoracic spine are the cause of this type of emphysema, and the qualifying term "postural emphysema" is often used interchangeably with senile emphysema (14).

(*3*) *Compensatory emphysema* develops when a portion of the lung contracts due to atelectasis or scarring, or is removed surgically. The remaining portion of the ipsilateral lung, or even the contralateral lung with simultaneous shift of the mediastinum, becomes distended and occupies the space left free by the collapsed or removed part of the lung.

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(*4*) *Obstructive emphysema*, as understood up to a few years ago, denotes an emphysematous condition localized in a portion of a lung, caused by partial ball-valve obstruction of a lobar bronchus. Air is more easily inhaled than expelled and so an increased amount of air is trapped and expands the involved portion of the lung.

(*5*) *Interstitial emphysema* is not alveolar emphysema but, rather, is the condition where air escapes from the air sacs into perivascular and peribronchial interstitial spaces; it extends into the mediastinum, or may dissect the subpleural tissue to form subpleural blebs (19). The pneumatocele found in children with acute respiratory infection is probably a large unicameral or multicameral interstitial accumulation of air.

(*6*) *Chronic hypertrophic emphysema* is also called chronic substantial emphysema, chronic vesicular emphysema, sometimes inspiratory or expiratory emphysema (according to the theory adhered to), irreversible emphysema, functional or structural, or large-lunged emphysema. This is the common type of emphysema which occurs most frequently in men and is encountered in 2 to 5 per cent of all autopsies. The chest is widened and the lung voluminous, and it does not collapse on opening the chest; the air sacs are dilated and the alveolar walls atrophic and often broken. The term "hypertrophic" originally denoted the voluminous appearance of the lung but is misleading because microscopy reveals atrophy of the structures. Convincing clinical evidence has been assembled in recent years that partial obstruction of small bronchi is a basic factor in the pathogenesis of this type of emphysema and the term *obstructive emphysema* is now often used for it. This is unfortunate because the term has been used for those localized forms of emphysema due to obstruction of larger bronchi, as mentioned above. If it is believed that the present theory of its pathogenesis ought to be indicated in the name of the disease, one might use the term *generalized peripheral obstructive emphysema* as opposed to the localized emphysema caused by obstruction of central bronchi. It seems preferable to retain the old commonly understood terms: chronic, substantial, or hypertrophic emphysema. As only the last-named condition will be discussed in the present paper, it will be designated simply as emphysema.

PATHOLOGY AND PATHOGENESIS

Pathologists noted long ago the great discrepancy between the clinical signs of pulmonary emphysema and the post-mortem findings. Cabot (4) showed the extent of this discrepancy by the disillusioning figures obtained at the Massachusetts General Hospital. Of 12 cases diagnosed as pulmonary emphysema, only 3 showed post-mortem evidence of it; while, of 153 cases recognized at post-mortem as having pulmonary emphysema, only 7 had been so diagnosed during life. In the face of these facts, Cabot gave up as hopeless the clinical diagnosis of pulmonary emphysema. More recently, in his Goulstonian lecture, Christie (5) comments in the same skeptical vein. Reporting an analysis of 72 cases studied at post mortem, he states: "The only conclusion that can be drawn from these series of cases is that the signs of emphysema are unreliable, —they may be absent in patients suffering from the disease, and are not uncommonly present in patients without emphysema." He believes that "It is those with little clinical experience who think they have a clear conception of the diagnosis of emphysema," and, it might be added, think they have a clear conception of the pathogenesis of emphysema.

Two basic misunderstandings have caused persistent confusion about the pathogenesis and diagnosis of emphysema (18):

1) It is usually taken for granted that 'structural emphysema' and clinical emphysema are identical and coterminous. In fact, they are two distinct, though related, conditions. *2*) Pulmonary emphysema is generally looked upon as a distinct clinico-pathologic entity. In fact, however, emphysema of the lungs is always but a secondary manifestation resulting from other primary conditions of the lung, the bronchi, the pleura, heart, or chest.

More recent investigations of the pathophysiology of emphysema have greatly contributed to the understanding of the fully developed condition; however, its pathogenesis is still rather obscure. While it is not the purpose of this presentation to examine all the theories of the pathogenesis of hypertrophic emphysema, a few theories will be mentioned and commented upon.

The theory based on bronchial obstruction has the most advocates. Laënnec (15), in his treatise of 1819, contended that emphysema begins with a catarrh of the bronchus. The bronchus being obstructed by mucus, a greater respiratory effort is necessary and, since the forces of expiration are weaker than those of inspiration, the expulsion of air is impaired. There has been much debate about the validity of this theory and there have been schools of thought favoring an inspiratory or expiratory obstruction, respectively. Kaltreider (13) recently presented inspiratory obstruction as an accepted fact. However, Laënnec's basic conception of bronchial obstruction is now generally accepted as an outstanding probability, principally on clinical grounds. Nevertheless, the discussion of the detailed mechanics of bronchial obstruction goes on. Gordon (8) finds fault with all theories advanced so far. Kountz and Alexander accept bronchial obstruction of the expiratory type as the predominant cause of emphysema; however, they do not reveal how it is brought about and how it works. Christie regards obstruction as the most obvious cause of emphysema. Apparently dissatisfied on physical grounds with the theories advanced so far, he continues,

that almost all cases of emphysema have a long-standing history of chronic bronchitis or asthma, or both, and this is also true for emphysema in horses and cattle. The effect of cough and bronchial spasm on the lung, and their mechanism, are therefore of primary importance in any discussion on the etiology of this disease. The mechanism of cough is simple.

Christie's detailed hypothetical analysis of the mechanism of cough is not convincing and evokes disagreement from Gordon with whom we concur.

GORDON'S THEORY OF GENERALIZED COMPENSATORY EMPHYSEMA

The theory of Gordon, envisaging hypertrophic emphysema as a special instance of compensatory emphysema, deserves broader discussion. The theory of compensatory emphysema appears to be well founded. When pulmonary tissue is destroyed or shrinks, or is surgically removed, the neighboring distensible parenchyma expands to fill the space left free. Localized compensatory emphy-

sema can readily be observed microscopically in the neighborhood of small pulmonary scars after tuberculosis, focal pneumonia, or chronic atelectasis. This distention in its gross appearance is commonly observed roentgenographically in cases of a collapsed lobe or after lobectomy. The distended lung will probably retain its resilience for a period of time. As the state of overdistention persists, however, the resilience may be lost and atrophy of the parenchymal structures may occur. Thus histologic changes indistinguishable from the findings in hypertrophic emphysema result. Thoracic surgeons have been concerned over the possibility of this compensatory distention after pneumonectomy giving rise to hypertrophic emphysema, and have conducted experiments to discover whether such sequelae would occur. Adams and Livingstone have come to the conclusion that true hypertrophic emphysema does result. Longacre and Johansmann (16) found early hypertrophic changes if the operations were performed on adult dogs. In this instance of compensatory emphysema, the pathogenetic sequence of events appears to be clear. There is stretching and overdistention of the tissue due to external pull. Owing to the scars or other sequelae of the preceding disease or surgical procedure, there is often associated impaired ventilatory movement of the distended parenchyma. If these conditions are allowed to persist for a long time, the elastic tissue will suffer, as any elastic tissue will do when it is overstretched, and irreversible structural damage becomes evident.

This clear sequence of events in the case of compensatory emphysema, on the one hand, and many untenable theories of hypertrophic emphysema on the other, have induced Gordon to consider hypertrophic emphysema as a special case of compensatory emphysema. He assumes bronchiolar obstructions in bronchitis or asthma to be the plausible cause in the mechanics of emphysema. Gordon suggests that it is unlikely, except in rare instances, that all bronchioles are constricted at the same time and to the same extent. Some bronchioles will be severely contracted, others less so, and some probably not at all. During inspiration, more air will enter the wider tubes than the narrower, hence the alveoli communicating with the less obstructed bronchioles will inflate more quickly than the others. A stage will arise when these less obstructed alveoli have reached their normal distension, while the others are only partially filled, and accordingly the total lung volume has not yet reached the capacity that it should have at the end of a normal inspiration. Any further inspiratory effort will obviously lead to overdistention of the more normal alveoli. Probably the bronchioles that are more obstructed at one time are less so at another, so the majority of the alveoli will be at one time or another overstretched, with eventual loss of elasticity and resultant hypertrophic emphysema. This assumption of alternating transient obstruction also takes care of the otherwise contradictory observation that in emphysema no bronchial obstruction or stricture is found; and, moreover, the bronchi are usually dilated; hypertrophic emphysema is usually found to be associated with cylindrical bronchiectasis of moderate degree. Gordon's theory sounds most convincing. It explains the simultaneous occurrence and close topical arrangement of atelectasis and emphysema. It also appears to be readily applicable in several instances, such as the "progressive

idiopathic pulmonary fibrosis associated with emphysema" by Hampton (10); or the true interstitial pneumonia or fibrosis, both acute and chronic; and in emphysema developing in a pneumoconiotic lung. Thus compensatory emphysema, conceived as a spatial adjustment to local conditions, may become more or less generalized provided that the causative process, in those instances scarring and shrinking, occurs in a disseminated generalized pattern. Nevertheless, if one attempts to visualize lungs with evenly distributed emphysematous changes without gross atelectasis and scarring, it is difficult to understand this homogeneity to be the result of a consequence of transient and shifting obstruction and reopening of bronchioles.

The clinical and morphologic pictures, as well as the functional disturbances, both respiratory and circulatory, have been thoroughly studied in fully developed emphysema. However, the immediate mechanism of the pulmonary distention is still obscure. We believe that there is not one single mechanism to explain all types of cases, as there is not one particular shape of chest associated with hypertrophic emphysema. Nevertheless, we hope to fill one gap in the train of events that has caused much difficulty in the past by presenting a physical calculation and a few roentgenologic observations.

A FEW PHYSICAL AND PHYSIOLOGIC PREMISES

Elasticity is the ability of matter to return to its original shape after extension, compression, twisting, or other forms of distortion without being permanently deformed. The elasticity of a body depends upon the nature of the matter composing it. A rubber band, for example, does not have as great an elasticity as a steel spring, for the elastic band, after subjection to great extension, does not regain its original shape, but is noticeably longer after such stretching than before. A brass spring, on the other hand, shows practically no deformation after stress is removed. Gases and liquids are perfectly elastic. The *common language* omits some features of this physical definition and adds two other modifying qualities, namely, the ease with which such deformity can be brought about and the degree of this deformity. In layman's understanding, a rubber band is more elastic than water or a piece of steel. In order to avoid misunderstanding, the term, elasticity, will not be used here but, instead, resilience of the lung or springiness. There are more reasons for avoiding the term, elasticity. The collapse of the chest and lung during expiration is often presented to be solely due to the "elasticity" of the lung, with particular emphasis on the elastic tissue elements. This is not entirely correct. In this respect the term "elastance," introduced by Bayliss and Robertson (2), is useful to distinguish between elasticity as a property of a substance and "elastance" as the property of a system or mechanical arrangement.

Both pleural layers are in close contact with each other because of the atmospheric pressure from inside. They do slide along each other but cannot separate from each other under any normal or pathologic condition except for the entrance into the pleural cavity of another medium, such as air (pneumothorax) or fluid (transudate, exudate, blood). Thus, every movement of the

chest wall is fully transmitted to the lung, and any movement of the lung carries with it the chest wall.

The chest wall is moved by the striated respiratory muscles, normal and auxiliary, the diaphragm, and the abdominal muscles. There are added the influences of gravity, the resilience of the structures of the chest wall, and the intra-abdominal pressure.

The lung itself is directly influenced by the elastic fibers of the bronchoalveolar network, the smooth bronchial and alveolar muscles, and the surface tension between air and the moist alveolar wall.

Elastic fibers: Von Neergaard and Wirz (20) found in experimental studies that the retraction due to the elastic structures makes up 25 per cent to a maximum of 30 per cent of the total retractile capacity of the lung.

Smooth muscle: The function of the extensive muscular systems along the bronchi down to the respiratory bronchioles is not yet fully elucidated. There is little doubt, however, as to the tonic action of the muscles as evidenced by pharmacologic effects on the bronchi caused by adrenalin, ephedrin, papaverin, and similar drugs, and viscerobronchial reflexes (17, 22, 3). Moreover, there is good suggestive evidence that the muscles take active part in the expansion and recoil of the lung during quiet respiration by rhythmic contraction and relaxation (electrobronchographic studies by Luisada).

Surface tension: Of greatest interest are von Neergaard's studies on surface tension, which is operative at the contact between the moist alveolar wall and the alveolar air. The thin film of moisture lining the alveolar cavity tends to contract the alveolar cavity by virtue of molecular attraction. Von Neergaard and Wirz compare this phenomenon with the tendency of soap bubbles still hanging on the straw to contract. The retraction due to surface tension is a function of the radius of curvature of the alveoli. This radius is small in the relaxed condition and causes a considerable surface tension. In the expanded state, however, the radius is long and the effect of the surface tension becomes small; it is even more so when the air sac is overexpanded. This means a considerable deficit of the contractile and expulsive capacity of the overexpanded lung, long before there is any possibility of structural damage.

It is worthy of comment that there is another factor which greatly influences the resilience of the lung. The plasticity in shape and size of hollow viscera depends mainly upon frictionless emptying and refilling of the organs with air or fluid. For example, if a solitary, noninflammatory gall stone becomes lodged in the cystic duct, the gall bladder will fail to contract due to the obstruction which prevents the outflow of bile even if the muscles and elastic elements of the bladder are functionally intact. Similarly, patency of the bronchial passages is a prerequisite to the normal respiratory play of the lung; any, though partial, obstruction of these passages interferes with this play. The respiratory changes of the intrapleural pressure in emphysema as found by Paine (21), and Dean and Visscher (6), demonstrating impaired inspiratory distensibility and expiratory recoil, point to difficulties of inflow and outflow in addition to the loss of structural elasticity.

These facts about pulmonary dynamics have been mentioned in order to recall that the system of elastic fibers is only one of several factors controlling the respiratory dynamics and perhaps not even a dominant one.

ROENTGENOLOGIC OBSERVATIONS

During inspiration, the bronchi are stretched and they become longer and wider. During expiration they recoil and become shorter and narrower. The fact of elongation is self-evident; the lung is stretched and with it the imbedded structures such as bronchi and blood vessels are subject to the same morphologic derangement. The inspiratory dilatation of the bronchi is not as self-evident. From our experience with elastic tubes, we would expect elongation to go hand in hand with narrowing. However, it has been shown roentgenographically (11) and also by bronchoscopy that the bronchial lumina widen on inspiration. Reflex neuromuscular actions have been suspected by some; however, it seems that the widening and narrowing are mainly, if not exclusively, passive effects on the bronchial walls. The stretching of the lung caused by the active expansion of the chest is transmitted to the bronchi not only in their longitudinal direction, but also all around their circumference through the plastic parenchyma. It is possible that there is another factor too which contributes to changes in the width of the bronchial lumen, particularly in those larger bronchi where a rather rigid cartilagenous skeleton of the wall would appear to inhibit too much of a change in transverse direction. If the bronchus is stretched, the mucous membrane and the submucous tissues are also stretched, flattened, and thinned out; if the bronchus retracts, the mucous membrane heaps up and becomes wider, thus narrowing the free lumen. Anatomic findings of circular mucosal folds in bronchi within atelectatic areas seem to support this assumption.

Whatever the underlying cause or causes may be, the bronchi widen and arrow during inspiration and expiration, respectively, as can be clearly seen on bronchograms taken in inspiration and expiration.

Normal inspiration is performed by forceful muscular action which provides a sufficient pressure gradient to draw in the air. Normal expiration occurs mainly by relaxation of the muscles, leaving it to gravity and to the resilience of the chest wall and lung to recoil. The pressure gradient is smaller. However, expiration lasts longer than inspiration. The slower rate of the air current, due to the smaller gradient, and the smaller lumen of the bronchi are compensated by shorter bronchi, smaller dead space, and the longer duration of the expiratory phase. Thus the full amount of air inhaled is blown out. In healthy subjects, the individual type of respiration apparently is fully adjusted to the anatomic arrangement and respiratory variability of the bronchi. In order to understand better the changes which occur during bronchitis, we may consider a gross pathologic situation. Valve mechanism in bronchi has been explained by Jackson (12). Here we are interested only in ball-valve mechanism. It is generally acknowledged that a respiratory disturbance leading to obstructive emphysema does not presuppose a pathologic situation similar to a mechanical ball-valve device. As a matter of fact, such a fluctuant foreign body or polyp is

an extremely rare occurrence. The ball-valve effect is usually produced in a quite different way and is made possible by the respiratory change of width of the bronchi.

A simple hypothetical example may illustrate this effect (figure 1). A bronchus of 6 mm. in width in inspiration narrows down to 5 mm. in expiration. A growth, 2 mm. in height, sessile on the wall, develops; the diameter is thus narrowed to 4 mm. in inspiration and to 3 mm. in expiration. If one simplifies this system by assuming that similar gradients prevail during inspiration and

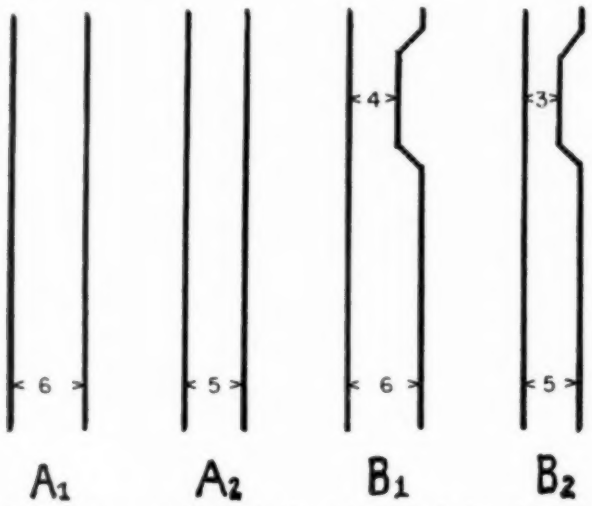

FIG. 1. Schematic representation of the change in width of a bronchus during respiration. A_1, inspiration, A_2, expiration: the bronchial diameter changes at a ratio of 6:5. B_1 and B_2 show the same bronchus with a sessile growth at its wall. At the site of the narrowing the respiratory change of diameter occurs at a ratio of 4:3.

expiration, also eliminating other variables, one may apply the physical rules for streamline flow in tubes, i.e., Poiseulle's formula, thus arriving at the following approximate figures.

The normal bronchus, 6 and 5 mm. in width, respectively, is able to transmit during expiration about one-half the amount of air passed during inspiration for an equal unit of time, representing a ratio of 1:2. The bronchus with the narrowing growth, having a width of 4 and 3 mm., respectively, is able to transmit during expiration only about *one-third* of the amount of air passed during inspiration for an equal period of time, making a ratio of 1:3. This deficit in expiration can be compensated for by increasing the pressure gradient and prolonging the expiratory phase. Both mechanisms occur physiologically in bronchitis and asthma. While normal respiration with its prolonged expiratory phase compensates for the morphologic mechanical changes, this delicately regulated mechanism is apt to be thrown off balance through any abnormal narrowing

which augments the resistance during expiration. A condition of decompensation sets in characterized by retention of air which prevents the lung from returning to its normal relaxed condition during and after expiration.

The anatomic changes in bronchitis produce conditions of similar nature. The mucous membrane is swollen and a film of viscous secretion covers the bronchial wall, both of which conditions are apt to narrow the bronchial lumen. Therefore, the expiratory dyspnea is encountered as a common sign in this condition and is especially prominent in children where the lesser degree of pulmonary distention fails to keep the bronchi patent as efficiently as the greater pulmonary stretching does in the subject of middle age. In addition, a bronchospastic component is very common in children even in the absence of true bronchial asthma. As has been shown above, this narrowing shifts the inspiration-expiration ratio of the bronchial diameters unfavorably toward expiratory stenosis. While the inspiratory obstruction can be compensated for by a more forceful inspiratory effort, expiratory difficulty is bound to become manifest.

The by-pass-valve mechanism in bronchitis is greatly magnified by a phenomenon hardly anticipated. In the course of bronchographic studies on bronchial physiology, we have made roentgenograms in inspiration and expiration in healthy subjects. Invariably, the following occurred: When just enough opaque oil had been injected to deposit a thin lining on the wall of the bronchi of the third, fourth, or fifth order in inspiration, the bronchial lumen remained patent and permitted free passage of air. Roentgenograms made in expiration showed quite a different picture. The bronchi were shorter and narrower, as expected. Moreover, the oil formerly spread as a thin film along the bronchial walls was heaped up, the same amount of oil spread over a smaller surface, and in several places the oil formed bridges from wall to wall, completely filling the lumen. Often there were air bubbles caught between these bridges. In some places, the effect of the surface tension manifested itself even more by narrowing the bronchial lumen (figure 2). It is not believed that this phenomenon indicates a pulling in of the entire bronchial wall or a sphincteric contraction but, rather, the appearance has been interpreted as the effect of a heaping up of the loosely attached mucosa (7).

In bronchitis and asthma there is increased production of secretion of various degrees of viscosity. In addition, there is often impairment of the action of the ciliated epithelium, thus adding to the accumulation of secretion. The degree of viscosity and the amount of secretion will determine the size of bronchi where this phenomenon of bridging in expiration may occur. However, there is no doubt that it is bound to occur. The power of capillarity and surface tension provide a by-pass-valve device of great effectiveness. During inspiration the bronchus is wide and patent and the secretion spreads as a thin film along the wall. In expiration the bronchus is shorter, narrower, and the secretion forms strong locks. The air taken in during inspiration is trapped until ciliary action or a cough removes those blocks. These observations represent the objective visualization of the expiratory obstruction, probably initiating the trapping of air, which has been postulated by many clinicians.

As a consequence of the inhibited expiratory emptying, the chest and lung

cannot collapse normally. Because of impaired hemo-respiratory exchange or reflex mechanisms, hyperpnea may set in, causing the successive inspirations to be more forceful and the expiratory phase not properly prolonged, so that further widening of the chest results. This labored breathing may lead to the condition of acute pulmonary emphysema or *volumen pulmonum auctum* as seen in an asthmatic attack. (We omit here a special discussion of bronchospasm, so prominent in asthma; its pathogenetic effect is very similar to any other narrowing of the bronchial lumina).

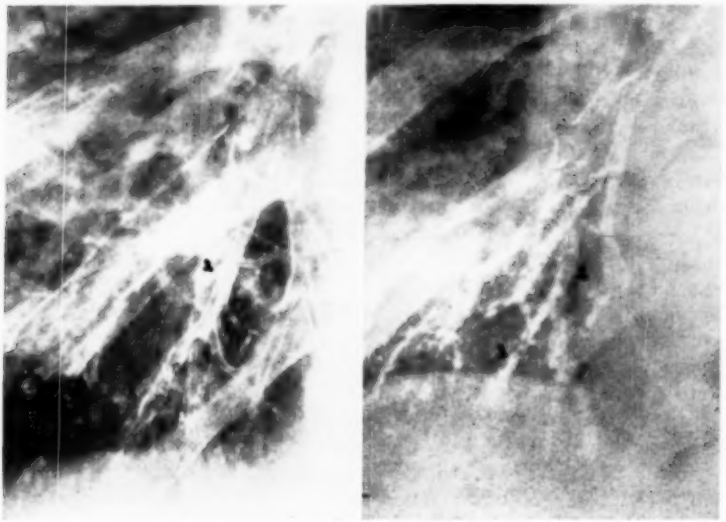

FIG. 2. Bronchogram in a normal subject. Reproductions in natural size showing a portion of the right lower lung field both in inspiration and expiration. A, inspiration: the bronchi are lined by a thin film of opaque oil. B, expiration: the figures 1 and 2 mark identical bronchi. They are shorter and narrower. Columns of oil, interrupted by air bubbles, fill them completely (retouched).

To express it in Laënnec's (15) words:

More air is inhaled through the 'tumid state of the bronchial membrane and the sputa' than is expelled. Succeeding inspirations, or at least such of them as are energetic, introduce a fresh supply of air into the same cells, and thereby necessarily occasion this dilation; and provided the obstruction is of some continuance, the dilated condition of the cells will be rendered permanent.

The expansion of the lung is limited and the lung protected from tearing by the maximum expansibility of the chest and the strength of its structures. How far the inspiratory effort may go is demonstrated by bilateral tears of the sternocleidomastoid muscles observed in drowning individuals (23). The inspira-

tory pull acts more or less evenly upon the whole lung, provided that there are no extensive intrapulmonary scars or pleural adhesions to prevent smooth sliding of the lung along the chest wall. During expiration the air chambers and lobules, the ductal system of which is not blocked, will easily empty, while those with an obstructed bronchus will stay filled. This process endlessly repeated with changing degrees of bronchial obstruction is apt to dilate markedly the alveolar sacs and to overstretch their structures.

The acutely, and even more so, the chronically emphysematous lung is found pathologically to be ischemic and dry, even before any destruction of alveolar walls or obliterative arteritis is noticeable. The capillaries apparently are compressed and the alveolar walls thinned by the increased intra-alveolar pressure. The ischemia is one of the reasons why the emphysematous lung, even in a case of obstructive emphysema due to a recent bronchial obstruction, appears more translucent roentgenographically. The ischemia, in addition to the constant pressure, may lead to permanent structural changes, to atrophy of the alveolar walls, and to coalescence of adjacent air chambers or, in Haldane's (9) words, ischemia and "anoxia not only stop the machinery but wreck the machinery."

COMMENT AND SUMMARY

In a review of different types of emphysema it is found that the common form, the hypertrophic or substantial emphysema, is almost generally considered to be due to some kind of bronchial obstruction. Therefore, it has been spoken of recently as obstructive emphysema. The writer recommends the retention of the traditional names, hypertrophic or substantial emphysema, because the term obstructive emphysema has been used for another condition, the emphysema occurring in partial obstruction of a large bronchus, supplying one lung, a lobe, or lobar segment. In a review of the factors controlling the expansibility and resilience of the lung, it is recalled that the structural elasticity of the lung contributes but a part of the total resilience, probably not more than 25 to 30 per cent. The remainder of the expansibility is provided by the resilience of the thoracic and abdominal wall and gravity and surface tension at the moist alveolar surfaces. In addition, patency of the ductal systems is a prerequisite of free expansion and collapse of the lung.

The decrease of the intrabronchial pressure gradient and the narrowing of the bronchi during expiration in normal conditions slow down the air flow during this phase. The longer duration of expiration compensates for this delayed evacuation. Every additional narrowing of the air passages is apt to act like a ball-valve and cause retention of air; such narrowing may be caused by swelling of the mucosa or bronchospasm. Furthermore, bronchographic observations with opaque oil demonstrate that a bronchus presenting a free lumen during inspiration may be completely blocked by bridging oil droplets during expiration. The same phenomenon apparently occurs in bronchi of various caliber during asthma and bronchitis, due to increased production of mucus or secretion. Thus the expiratory obstruction, postulated as the causative functional factor in

emphysema, has been visually demonstrated. The hypothetical assumption that structural changes in the pulmonary parenchyma, such as degeneration of elastic tissue, initiate the development of substantial emphysema has not been supported by convincing evidence. On the other hand, the anatomic patency of the smaller bronchi and alveolar infundibula seem to contradict the assumption of obstruction. The presented observations provide a missing link between these facts and the accepted theory of the pathogenesis of substantial emphysema.

SUMARIO

Observaciones Relativas a la Patología del Enfisema Sustancial (Hipertrófico) Crónico

Un repaso de diversas formas del enfisema revela que la más común, el enfisema hipertrófico o sustancial, está considerado casi generalmente como debido a algún género de obstrucción bronquial, por lo cual ha sido denominado recientemente enfisema obstructivo. El A. recomienda la retención de los nombres tradicionales de enfisema hipertrófico o sustancial, dado que el término de enfisema obstructivo ha sido utilizado para otro estado, o sea el enfisema consecutivo a la obstrucción parcial de un bronquio grande que sirve un pulmón, un lóbulo o un segmento lobular. En un repaso de los factores que gobiernan la expansibilidad y elasticidad del pulmón, recuérdase que la elasticidad estructural de dicho órgano sólo constituye parte de la elasticidad total, probablemente no más de 25 a 30 por ciento, en tanto que el restante lo suministran la elasticidad de las paredes abdominal y torácica, la gravedad y la tensión superficial en las superficies alveolares húmedas, siendo además la permeabilidad de los diversos conductos prerrequisito de la libre expansión y aplastamiento del pulmón.

La disminución de la pendiente de presión intrabronquial y el estrechamiento de los bronquios durante la expiración retardan el paso del aire durante esa fase en condiciones normales. La mayor duración de la expiración compensa ese retardo en la evacuación. Todo nuevo estrechamiento de las vías aéreas es susceptible de actuar como una válvula de bolas y ocasionar retención de aire, pudiendo deberse dicho estrechamiento a edema de la mucosa o a espasmo bronquial. Además, las observaciones broncocópicas realizadas con aceite opaco demuestran que un bronquio que presenta una luz despejada durante la inspiración puede estar absolutamente ocluído por un puentecillo de gotas de aceite durante la expiración. El mismo fenómeno tiene lugar aparentemente en los bronquios de varios calibres durante el asma y la bronquitis, debido a la mayor producción de mucosidades o secreción. La obstrucción expiratoria, señalada como factor funcional etiológico del enfisema, ha sido, pues, visualizada. La hipótesis de que la aparición del enfisema sustancial es iniciada por alteraciones estructurales del parénquima pulmonar, tales como degeneración del tejido elástico, no está apoyada por datos convincentes. En cambio, la permeabilidad anatómica de los bronquios más pequeños y de los infundíbulos alveolares parece contradecir la suposición de obstrucción. Las observaciones expuestas agregan

un eslabón más a la cadena que une los datos recopilados con la teoría aceptada para explicar la patogenia del enfisema sustancial.

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A STUDY OF THE RELATION OF NUTRITIONAL STATUS TO PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

Much investigation, both clinical and experimental, has been carried out in an attempt to elucidate the widely accepted principle that nutrition is an important factor in the treatment of human tuberculosis. Clinical studies have been chiefly concerned with people on restricted diets during times of war (1, 2, 3). The recent work of Dubos and Pierce (4) with mice supports the clinical observations by demonstrating that a correlation exists between diet and survival time of mice infected with experimental tuberculosis. Further animal experimentation is needed to evaluate the effect of specific deficiencies or harmful factors in diet, and could help to guide new investigation and therapy.

Review of Literature

Metcoff and associates (5), Cannon (6), and Sako (7) have reported that a relationship exists between protein intake and antibody formation and resistance to infection in general. Clinical observation has shown that either poor utilization or insufficient intake of nitrogenous food lowers resistance to tuberculosis (8). In other studies in humans, attempts have been made to show correlation between specific nutrients and the response of the body to tuberculosis, with emphasis thus far in the fields of protein, vitamin, and calcium metabolism.

Vitamin A has been called the anti-infective vitamin, which is perhaps unfortunate because of the exaggerated implication of the term. The role of vitamin A in preventing infection appears to lie entirely in its function in maintaining the integrity of epithelial tissues. Its deficiency may cause keratinization and resultant infection of the conjunctiva, oral and nasal mucosa, and other epithelial tissues. On the other hand, the present knowledge does not warrant the conclusion that vitamin A deficiency predisposes to development of a specific infection such as tuberculosis, or that increased vitamin A intake has any curative effect in this disease (9). Moore (10) determined the liver stores of vitamin A in 1,000 autopsies following death from various causes. There was wide variation in the vitamin A stores of patients dying either of disease or accident. The calculated mean vitamin A store in cases of tuberculosis of all types revealed a moderately low level, which was characteristic of a large number of pathologic states, including cancer, syphilis, peptic ulcer, hypertension, gall bladder disease, and cerebral hemorrhage. On the other hand, septic diseases of all types had very low stores. Getz, Westfall, and Henderson (11) studied the nutritional status of a group of 450 patients seen at an outpatient chest clinic in a metropolitan area. Of these patients, slightly over half were nontuberculous, and the remainder had pulmonary tuberculosis in various stages and degrees of activity. The study was based on determinations of blood concentrations of vitamin A, carotene,

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ascorbic acid, albumin, globulin, phosphorus, calcium, phosphatase, and hemoglobin; and also the erythrocyte sedimentation rate. These investigators concluded that the blood levels of vitamin A were similar in the nontuberculous subjects and in those with inactive tuberculosis but, when active tuberculosis was present, the blood level of vitamin A was low. The report included no correlation of the observed values with the dietary intakes of the patients. The apparent low level of vitamin A in active tuberculosis is thought by some workers to be the result of faulty absorption. Breese, Watkins, and McCoord (12) performed a vitamin A "absorption test" on 17 tuberculous patients who also had gastrointestinal symptoms. They found some impairment in rate of absorption over a period of twelve hours. The degree of impairment roughly paralleled the severity of the symptoms. Unfortunately, they present no data on tuberculous patients without gastrointestinal symptoms.

The relationship between vitamin C and infection is not clearly established, but febrile conditions usually cause a decrease in serum levels and urinary output. Vitamin C has been frequently investigated in its relation to tuberculosis, and some workers have considered that there is an increased requirement in the presence of the disease. Other chronic diseases usually associated with fever also may have an increased vitamin C requirement (13). Sweany and his associates (14) showed, by means of tissue saturation tests in patients with tuberculosis, that there was a rough correlation between severity of the disease and degree of tissue saturation with vitamin C. They also analyzed 32 bodies at autopsy for total vitamin C, and found that body stores were extremely low following long, severe tuberculosis. Chiang and Lan (15) determined ascorbic acid urinary outputs and blood levels of 100 outpatients at a tuberculosis clinic in China, using 10 employees (technicians and doctors) as controls. They found that the patients showed much lower amounts in both blood and urine than did the controls. They also found that some of the advanced cases showed evidence of diminished amounts in body tissues by one of the "saturation tests." Kaplan and Zonnis (16) studied ascorbic acid blood levels of 240 patients in a tuberculosis sanatorium. They found a correlation between stage of disease and blood level. On the other hand, Webb, Storwick, and Olson (17) performed saturation tests on 6 patients with far advanced tuberculosis with moderate to severe symptoms who had been on a 100 mg. daily supplement of vitamin C. Their results were similar for the patients and controls. They also determined the blood levels on 150 sanatorium patients with all stages of pulmonary tuberculosis who were on a supplement of 100 mg. of ascorbic acid daily. The average levels for all stages were well above 1.0 mg. per 100 cc., and there was no correlation between serum level and degree of tuberculosis. The patients with fever had an average level of 0.83 mg. per 100 cc. Getz, Westfall, and Henderson (11) found low blood levels of ascorbic acid in a large percentage of both tuberculous and nontuberculous persons. The values they reported indicate little correlation between stage of disease and ascorbic acid deficiency. Eighty-one per cent of the nontuberculous group were below the so-called minimum standard of 0.5 mg. per 100 cc., while the percentages of active tuberculous cases below 0.5 mg. ascorbic acid per 100 cc. were, for the minimal, moderately advanced, and far advanced, 81 per cent, 63 per cent, and 87 per cent, respectively.

It should be pointed out that the investigations reviewed above on nutrition in human tuberculosis include little or no consideration of the dietary intakes of the patients. Nutritional status reflects, first and foremost, the diet of the individual. Only after this primary variable has been determined should studies of other variables affecting nutrition be made. With this principle in mind, the

present study was undertaken on a series of 187 patients and a few employees with pulmonary tuberculosis at the Hermann M. Biggs Memorial Hospital.

PLAN OF INVESTIGATION

Diet studies were first done on the subjects to determine whether the intakes of the patients were as adequate as those of healthy people. Following this, blood levels of specific nutrients were correlated with severity of disease.

The food intake of the group of patients was determined by selecting for study 25 patients who had been found to have low blood levels of carotene. It was thought that the average intake of the entire group would be at least as high

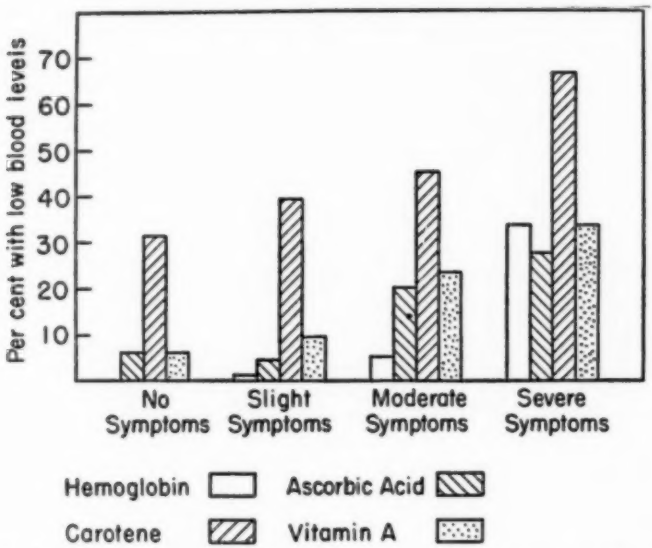

FIG. 1. Per cent of patients in each symptom class with inadequate blood concentrations of hemoglobin, ascorbic acid, carotene, and vitamin A.

as that of these 25, and it was the opinion of the hospital dietitian that the dietaries studied were representative of the whole group. The diet studies were done as follows: (a) A record of portions of food eaten at each meal was kept by the patient for a period of three weeks. (b) An interview type of dietary history was conducted on each of the patients by a trained nutritionist. (c) Food portions used in calculating the dietaries were determined by weighing the servings of three trays before each meal for seven days. The food records and diet histories were checked with each other, and thus a reasonable idea of the patient's diet was obtained.

For comparison with a nontuberculous group, similar studies were done on

17 employees of the hospital who had no evidence of tuberculosis. In addition, data were available on a group of 100 adults from a nearby farm and village population who represented a random sample of a larger group being studied in a regional nutrition survey. These individuals presented no evidence of pulmonary tuberculosis in their chest roentgenograms. Dietary studies made on this group

TABLE 1

Per cent Distribution according to Status and Stage of Tuberculosis

Percentage of cases in each blood-level group, classified according to status and stage of tuberculosis

PER CENT	NONTUBERCULOUS	APPARENTLY CURED TO QUIESCENT	ACTIVE		
			Minimal	Moderately Advanced	Far Advanced
Hemoglobin					
Total	(118)	(47)	(16)	(63)	(61)
Under 11 gm. per 100 cc.	1	0	0	2	10
11 to 12.9 gm. per 100 cc.	23	11	6	17	29
13+ gm. per 100 cc.	76	89	94	80	60
Ascorbic Acid					
Total	(118)	(47)	(16)	(63)	(61)
Under 0.4 γ per 100 cc.	10	4	12	8	10
0.4 to 0.6 γ per 100 cc.	16	17	6	8	17
0.7+ γ per 100 cc.	74	79	81	84	83
Carotene					
Total	(117)	(47)	(16)	(63)	(61)
Under 75 γ per 100 cc.	38	34	44	46	39
75 to 124 γ per 100 cc.	32	42	37	31	37
125 to 199 γ per 100 cc.	26	17	19	15	13
200+ γ per 100 cc.	3	6	0	6	10
Vitamin A					
Total	(116)	(45)	(16)	(60)	(53)
Under 30 γ per 100 cc.	6	6	0	10	20
30 to 69 γ per 100 cc.	81	68	68	50	58
70+ γ per 100 cc.	12	26	31	40	20

consisted of family food purchase and consumption records kept for a period of one week.

Serum determinations were done on all subjects according to the micro-methods of Bessey and Lowry (18, 19, 20, 21) and included determinations of hemoglobin, vitamins A and C, carotene, alkaline phosphatase, and total protein. The specimens of blood were taken from the patients in July 1948, from the employees in January 1949, and from the other 100 nontuberculous subjects in October and November 1948. This factor might conceivably result in a somewhat lower level of ascorbic acid in the subjects studied in the fall and winter, but the dietary studies done at the same time would not indicate a lower ascorbic acid intake in that group.

The tuberculosis patients were classified according to the standards of the National Tuberculosis Association as to clinical status, stage, and severity of symptoms. For facility in interpreting tables, some condensation of classes was done, so that in table 1 all inactive statuses (apparently cured to quiescent) are grouped together, while the active cases are separated into the three stages. The symptomatic classification is not included in table 1,

TABLE 2

Per cent Distribution according to Symptoms

Percentage of cases in each blood-level group, classified according to severity of symptoms

	NONTUBERCULOUS	SYMPTOM CLASS			
		No Symptoms	Slight Symptoms	Moderate Symptoms	Severe Symptoms
Hemoglobin					
Total	(118)	(50)	(102)	(20)	(15)
Under 11 gm. per 100 cc.	1	0	1	5	33
11 to 12.9 gm. per 100 cc.	23	8	19	35	33
13.0+ gm. per 100 cc.	76	92	81	60	33
Ascorbic Acid					
Total	(118)	(50)	(102)	(20)	(15)
Under 0.4 γ per 100 cc.	10	6	4	20	27
0.4 to 0.6 γ per 100 cc.	16	8	14	20	13
0.7+ γ per 100 cc.	74	86	82	60	60
Carotene					
Total	(117)	(50)	(102)	(20)	(15)
Under 75 γ per 100 cc.	38	32	39	50	66
75 to 124 γ per 100 cc.	32	40	39	30	27
125 to 199 γ per 100 cc.	26	20	15	15	7
200+ γ per 100 cc.	3	8	8	5	0
Vitamin A					
Total	(116)	(48)	(96)	(17)	(12)
Under 30 γ per 100 cc.	6	6	9	23	33
30 to 69 γ per 100 cc.	81	66	53	64	59
70+ γ per 100 cc.	12	27	38	12	8

but is shown in table 2, which includes all stages grouped solely according to severity of symptoms.

ANALYSIS OF DATA

The intakes of the 25 patients met the requirements of the Recommended Dietary Allowances in all nutrients studied except vitamin C and iron, and these were only slightly below the recommendations. The diets of the 17 employees were in general about the same as those of the patients save perhaps for a slightly higher average in vitamins C and A. The estimates of intake of the 100 rural adults showed approximately 50 per cent higher intake for most nutrients. However, this group had higher requirements because they were physically active individuals. Also, the method of diet study on this group was less accurate, and

probably gave higher values than actually occurred, chiefly because the factor of waste was not considered.

It can be seen from table 1 that there was little or no correlation between status or stage of tuberculosis and the blood levels of the factors studied. The possible exception was hemoglobin, which was lower in the far advanced cases than in the nontuberculous group. All stages of tuberculosis showed higher levels of ascorbic acid than the nontuberculous. Table 2, however, presents a different picture. Here, classification is according to symptoms (fever, cough, amount of sputum, weakness, malaise, et cetera). There was a close correlation between symptoms and the blood concentrations of all the nutrients studied. Total proteins are not recorded because nearly all were within normal limits. It should be noted that no single nutrient appeared to be affected more than the others, but there was a general trend downward in the blood concentration of all nutrients as the symptoms became more severe. Scatter-graph studies of the 25 patients with dietary determinations showed no correlation between symptomatic classification and intake of calories, vitamin A, or vitamin C, indicating further that low blood levels of these nutrients could not be due to diminished intakes.

DISCUSSION

It is beyond the scope of this paper to discuss extensively the significance of the blood levels of the nutrients here studied, or to indicate what levels should be considered adequate. There is yet much controversy in this field. It is believed by many workers that 0.7 mg. per 100 cc. of ascorbic acid should be regarded as the lower limit of safety, although the recent work of Krebs and his group in England (22) would tend to indicate a much lower level as entirely safe. Considerable fluctuation can occur with daily intake if the tissues are saturated, so that variations above 1.0 mg. per 100 cc. are of little significance. However, when the levels are low, this usually means that there is some degree of unsaturation, so that any new intake is quickly taken up by the tissues, maintaining a fairly constant low blood level. Plasma levels of carotene vary widely, and have been found by us to range from 50 to 400 γ per 100 cc.; but the lower limits of normal are usually thought to be around 75 γ per 100 cc. Plasma carotene changes rather slowly with variations in intake, and several weeks are required before a carotene-deficient diet is reflected by a drop in the plasma level. The plasma has been shown to reach a level of about 20 γ per 100 cc. within three months, where it remained for two years on a carotene-free diet (23). Vitamin A blood levels change even more slowly than carotene levels on a vitamin-A-deficient diet and show little day-to-day fluctuation, requiring a fairly large dose of the vitamin to produce any significant rise in the blood level. The vitamin A blood level roughly reflects the hepatic stores, and six months to two years are required to produce a depletion of these stores (23).

Serum alkaline phosphatase is elevated in a number of pathologic states, and its significance in a nutrition study is chiefly as an indication of poor vitamin D nutrition in children. Since the present study was done mainly on adults, and since very few abnormal levels were found, the phosphatase data are not

recorded here. Serum protein data are likewise not included in the tables, as very few abnormal values were found. Unfortunately no micro-method is available for determining albumin and globulin separately. Further work with more complete study of protein nutrition in tuberculosis is indicated. A comprehensive review of the problem of the evaluation of nutritional status by blood-chemical determinations can be found in the National Research Council bulletin on nutrition surveys (24).

The general low values of all nutrients in those patients with severe symptomatic tuberculosis warrants further study. The 25 patients whose diets were carefully studied are mostly patients with slight or moderate symptoms, and none with severe symptoms. For this reason we can furnish no data concerning the intakes of the acutely ill patients, and believe that further studies are needed in cases of this type with a view to correlation of food intake and serum levels. This may furnish further data as to whether disease or intake is the primary causative factor of the low serum levels. In the cases studied, there was little correlation between intakes and blood levels of vitamins A and C.

SUMMARY AND CONCLUSIONS

1. Studies were made on 187 adult patients with pulmonary tuberculosis at a tuberculosis hospital, and on 118 nontuberculous adults. Serum determinations were made of hemoglobin, vitamins A and C, carotene, alkaline phosphatase, and total protein. Detailed dietary studies were made on 25 patients and on 17 nontuberculous employees, with rough estimates of the diets of the other 100 nontuberculous adults.

2. The diets of the tuberculous and nontuberculous were fairly comparable in all nutrients and food types and, of the 25 patients studied who had no, slight, or moderate symptoms, there was no relation between severity of symptoms and food intake.

3. There was close correlation between severity of symptoms and diminution of blood levels of all nutrients studied. There was no correlation between stage of disease and blood levels.

4. This study indicates that when Recommended Dietary Allowances are met, tuberculosis is usually accompanied by normal blood levels of carotene and vitamins A and C, except in the presence of severe symptoms. Further investigation of patients with severe symptoms is indicated to determine whether their low blood values are a result of inadequate food intake, of the toxic febrile state, or are unique in tuberculosis.

SUMARIO Y CONCLUSIONES

Estudio de la Relación del Estado Nutritivo con la Tuberculosis Pulmonar

1. Los estudios aquí presentados fueron ejecutados en 187 enfermos adultos con tuberculosis pulmonar de un hospital para tuberculosos y en 118 adultos no tuberculosos. Hiciéronse determinaciones séricas con respecto a hemoglobina, vitaminas A y C, carotina, álcalis fosfatasa y proteína total. En 25 enfermos y 17 de los empleados no tuberculosos, verificáronse pormenorizados estudios

dietéticos, con cálculos toscos de la alimentación en los otros 100 adultos no tuberculosos.

2. Los régimenes dietéticos de los tuberculosos y los otros fueron bastante comparables en cuanto a todos los nutrientes y formas de alimento, y en los 25 enfermos estudiados, que no tenían síntomas o, si los tenían, eran leves o moderados, no había relación entre la gravedad de los síntomas y la ingestión alimenticia.

3. Hubo íntima correlación entre la gravedad de la semiología y la disminución de los tenores sanguíneos de todos los nutrientes estudiados, mas no hubo la menor correlación entre el período de la enfermedad y los tenores sanguíneos.

4. Indica este estudio que, si se suministran las raciones dietéticas recomendadas, la tuberculosis suele ir acompañada de niveles sanguíneos normales de carotina y vitaminas A y C, salvo cuando existen síntomas graves. Hállase indicada una investigación ulterior de los enfermos con síntomas graves para determinar si sus bajas cifras sanguíneas proceden de inadecuada ingestión alimenticia, del estado febril tóxico o específicamente de la tuberculosis.

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SIGNIFICANCE OF CHANGES IN THE CONTENT OF SERUM POLYSACCHARIDE DURING SENSITIZATION AND DEVELOPMENT OF TUBERCULOSIS[1,2]

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INTRODUCTION

A substance giving color reactions for polysaccharide has been demonstrated (1) to increase in human blood serum as tuberculosis progresses. It was identified as accompanying the α_2-globulin fraction of the serum. Furthermore, it appeared in the blood stream not only in tuberculosis, but also in other pathologic conditions apparently characterized by tissue destruction.

Because it appeared under such conditions, the substance was suspected to be of nucleic acid nature, since tissue breakdown could logically result in the release of such a substance. This hypothesis was strengthened when it was found that the tryptophane-perchloric acid reaction (2) seemed to be about six times as specific, in detecting the carbohydrate radical of the substance, as was the carbazole reaction (1). However, extended chemical investigation (3) did not lead to conclusive evidence that the substance was a true nucleic acid fraction.

A simple practical method was devised for its analysis (3), using only Klett readings for comparison, in lieu of a definite standard. This method, for short, was called the TA (for tryptophane-acid) method and this term has been used in this study.

During an investigation of the immunizing capacity of various tuberculin protein fractions in comparison with BCG, there was an excellent opportunity for following the changes in the serum polysaccharide constituent during the immunization processes, as well as during initial or subsequent infection with virulent tubercle bacilli. The immunizing effect of these protein fractions has been reported elsewhere (4).

Although the same or similar polysaccharide may appear in the serum as a result of other diseases, this study will show its prognostic significance in relation to uncomplicated tuberculosis.

EXPERIMENTAL

Methods

Rabbits were bled from the ear vein at specified intervals and the serum promptly removed, avoiding hemolysis of the blood cells. The serum was ana-

[1] From The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

lyzed by the TA method (3), as discussed above. The results were recorded as Klett readings in the tables.

TABLE 1

Tryptophane-Perchloric Acid (TA) Klett Values on Serum before and during Sensitization

GROUP	RABBIT NUMBER	TA (KLETT READINGS)					
		Normal	During Sensitization following Number of Injections				
			5	10	12	15	16
Controls	57	72 65					
	59	59 52					
	64	50 60					
	69	44 45					
	71	45 43					
	126	65 42					
	128	63 73					
	130	63 53					
	134	54 51					
	144	52 53					
	149	50 36					
	165	62					
	166	62					
	200	53					
		— —					
Average.....		56 53					
A	51	46	60			89	
	53	61		73		88	80
	56	45	39			51	
	122	49	65			77	83
	123	58	59			55	79
	135	54		64		68	
	137	31		53		84	
	138	46		82		106	
	145	40		67	83	85	
	152	37		47		79	80
	156	46		75		70	89
		—				—	
Average.....		47				77	
C	50	57		57		70	
	55	59	59			76	79
	58	49		62	56	62	68
	65	57	57			74	72
	68	54		46		60	
	124	57	55			61	
	132	60		55		57	
	133	51		52		67	
	148	54	57			69	70
	151	49		58		60	
	153	39		51		65	70
		—				—	
Average.....		53				66	

TABLE 1—*Continued*

GROUP	RABBIT NUMBER	TA (KLETT READINGS)					
		Normal	During Sensitization following Number of Injections				
			5	10	12	13	14
BCG	52	48	57			58	74
	54	56		91		71	
	66	43		44		59	
	67	49		50		65	
	70	47	53			76	51
	72	57	50			78	81
	129	58		68	73	50	
	131	57		68	74	60	81
	136	47		47		64	
	146	50		51		64	
	154	50		53		65	
	155	67	62			68	73
		—				—	
Average.....		52				65	

The rabbits were also weighed at regular weekly intervals. In the graphs illustrating this paper the first weight was recorded on the day of infection.

At autopsy an approximation was made of the per cent of the total lung volume occupied by tuberculous lesions. The lungs were also weighed.

Materials

The serum used was from rabbits in experiment 5 described in another publication (4). In that experiment one series of rabbits, which were controls, had no treatment prior to the intravenous injection of 0.00002 mg. of virulent bovine tubercle bacilli (Ravenel strain). Another series received 14 intracutaneous injections, each of 0.25 mg. of BCG, at weekly intervals prior to inoculation with the same dose of virulent tubercle bacilli. A third series received weekly injections of 10 mg. of protein A (to be described below) prior to infection; and a fourth series, weekly injections of protein C (see below). The injections of these proteins were given as follows: 6 intravenous, then one intracutaneous, 7 more intravenous, and 2 final intracutaneous injections.

Observations in a series of 7 humans vaccinated with 0.015 mg. of BCG will also be reported.

The A protein was a fraction isolated from unheated tuberculin (5). It had the lowest electrophoretic mobility of all the protein fractions; it was the most potent as a tuberculin in eliciting the skin reaction, per milligram of nitrogen, and also in producing the Arthus reaction. It was colorless in a solution of 1 per cent concentration and differed chemically from the C protein.

The C protein was also isolated from unheated tuberculin (5). It had a faster electrophoretic mobility than A, was less potent in the tuberculin skin reaction and in producing the Arthus reaction, and a solution of 1 per cent concentration had a deep amber color.

Results

Effect of sensitization on the TA value: Table 1 shows that the serum polysaccharide was significantly increased during the sensitization process (see average readings). This was especially conspicuous during the sensitization with the

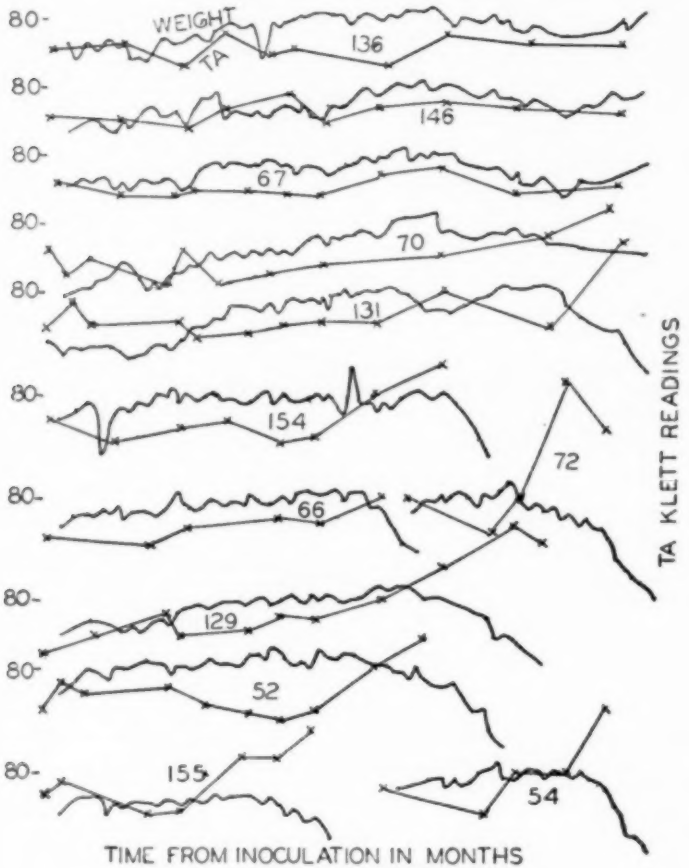

FIG. 1. Rabbits sensitized with BCG

A protein, where the average TA value at the end of 15 injections was considerably higher than that with any of the other fractions. This is logical in view of the fact that larger Arthus reactions with more necrosis were being produced with this fraction than with any of the other fractions.

The injections of the C protein caused definite indurated reactions, usually

without necrosis, and the BCG injections resulted in small ulcers which gradually healed. Injections of both of these, however, were accompanied by some rise in the TA values of the serum.

A group of humans also was studied. Their serum was analyzed for TA values, as well as by electrophoresis, before and two and three months following vacci-

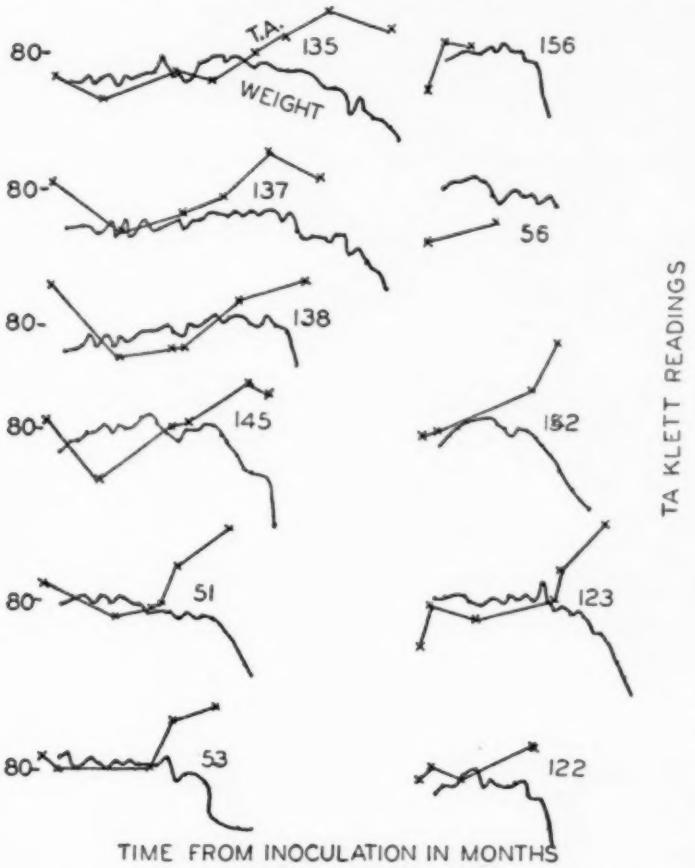

FIG. 2. Rabbits sensitized with A protein

nation with 0.015 mg. of BCG. Table 2 shows the results. No significant increase in TA value was found, and the only suggestive changes observed by electrophoresis were a small drop in the albumin and a possible slight drop in the β-globulin content at the two-month interval.

Effect of infection on the TA values: Figures 1, 2, 3, and 4 present the

correlation between the weights of the rabbits and the TA values of their serum. Each block on the abscissa of the graphs represents a period of one month. It is clearly shown that, when the TA value began to rise, the weight of the rabbit declined, and the decline continued rapidly until death occurred. The curves

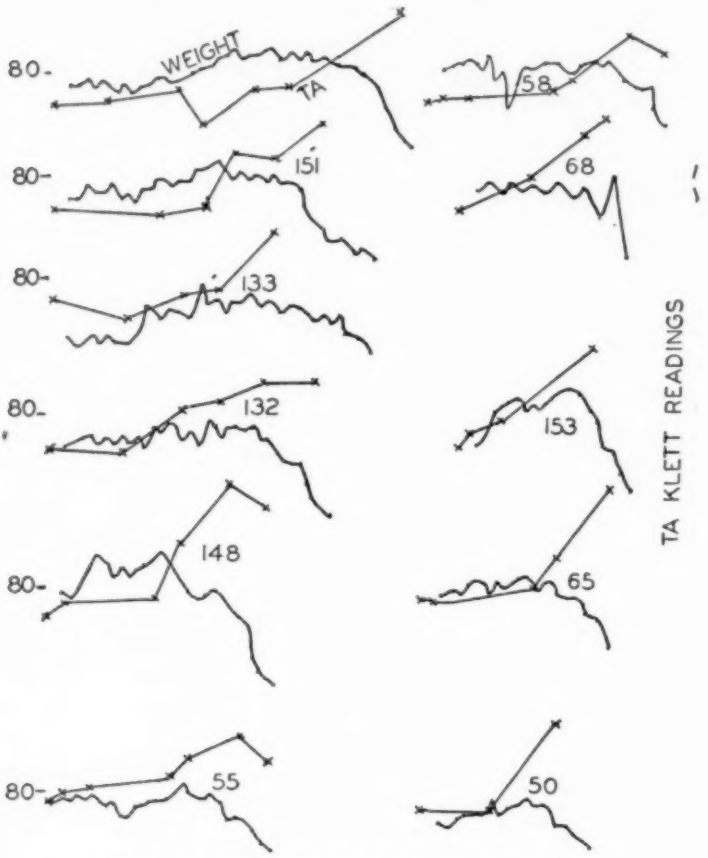

FIG. 3. Rabbits sensitized with C protein

of the control rabbits, which had no treatment prior to infection, do not differ significantly from the other curves in character. The curves for the rabbits vaccinated with BCG before infection present a strong contrast to the other curves, in that in some cases the weights and TA values continued indefinitely with no marked change. However, when a definite increase in the TA value did

occur, then the weight rapidly declined and the rabbit died with extensive tuberculosis. On the whole this change occurred relatively soon after infection in the A- and C-treated rabbits.

It appeared that in all cases when the TA value rose to a Klett reading of

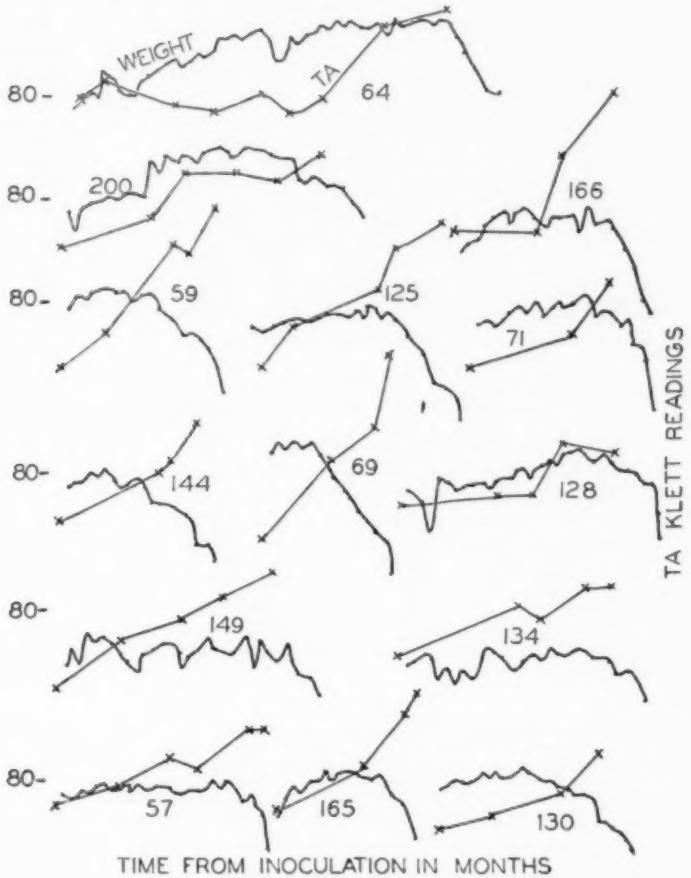

FIG. 4. Control rabbits

80 or over the prognosis was very bad. Smaller increases, not reaching this value (see rabbits Nos. 136, 146, and 70 in the BCG group), seemed to be compatible with recovery or survival.

With this limit in mind an analysis was made of the average number of days from inoculation until the TA value reached 80, and then of the number of days

TABLE 2

Effect of BCG Vaccination on Serum Components in Humans

SUBJECT	TIME OF BLEEDING	TA (KLETT READING)	TOTAL PROTEIN GM PER 100 CC.	GRAMS PER 100 CC.					A/G RATIO
				Albumin	Globulins				
					α_1	α_2	β	γ	
M.P.	Normal	42	7.8	4.2	0.76	0.73	1.04	1.00	1.2
	2 months*	39	7.1	3.8	0.70	0.74	0.97	0.95	1.1
	3 months	46	7.1	3.7	0.53	0.66	0.95	1.23	1.1
I.B.	Normal	66	7.6	3.9	0.64	0.87	1.18	0.93	1.1
	2 months	54	7.4	3.9	0.57	0.86	1.06	0.99	1.1
	3 months	61	7.0	3.7	1.12	0.80	0.62	0.77	1.1
D.A.	Normal	44	6.6	3.6	0.45	0.71	0.94	0.88	1.2
	2 months	46	6.2	3.3	0.54	0.60	0.84	0.92	1.2
	3 months	58	6.6	3.4	0.61	0.73	0.93	0.92	1.1
C.D.	Normal	64	7.2	3.6	0.67	0.73	0.96	1.23	1.0
	2 months	55	6.3	3.3	0.62	0.74	0.76	0.91	1.1
	3 months	66	7.1	3.8	0.67	0.75	0.97	0.95	1.1
M.A.	Normal	46	7.2	3.7	0.56	0.81	1.02	1.08	1.1
	2 months	44	6.4	3.4	0.51	0.67	0.86	0.95	1.1
	3 months	58	7.4	3.7	0.62	0.69	1.04	1.04	1.2
D.H.	Normal	70	7.3	3.7	0.66	0.92	1.27	0.80	1.0
	2 months	61	6.6	3.5	0.59	0.86	1.08	0.53	1.1
	3 months	83	6.8	3.3	0.68	1.09	1.01	0.68	0.9
S.D.	Normal	48	7.3	3.8	0.52	0.63	1.03	1.38	1.1
	2 months	47	6.9	3.7	0.46	0.68	0.87	1.16	1.1
	3 months	44	7.0	3.7	0.45	0.64	1.05	1.17	1.1

* Post vaccination.

TABLE 3

Prognostic Indication of Serum Values by Tryptophan-Perchloric Acid Method (TA)

GROUP	NUMBER OF RABBITS	DAYS FROM INOCULATION TO TA = 80		DAYS FROM TA = 80 UNTIL DEATH		TOTAL LONGEVITY DAYS		PER CENT LUNG TUBERCULOSIS		WEIGHT OF LUNGS IN GRAMS	
		Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
Controls	14	98	40 to 261	99	54 to 180	197	113 to 391	56	5 to 99	58	19 to 193
A Protein	11	85*	0 to 167 X	101*	65 to 139	178	96 to 301	51	2 to 95	51	25 to 122
C Protein	11	94	0 to 217 X	109	68 to 183	204	129 to 312	72	1 to 99	68	31 to 134
BCG	7	210	104 to 276	112	45 to 155	324	224 to 431	66	20 to 98	55	21 to 89

* Only ten rabbits were included in this average, since in one rabbit the TA never reached 80.

X In two rabbits receiving A protein and in one receiving C protein the TA had already reached 80 before inoculation.

from that time until death of the rabbit (See table 2). It is interesting that of 12 rabbits vaccinated with BCG prior to infection, so far only 7 have died, and among these the average time from infection until the TA value reached 80 was 210 days, in contrast to 85 to 98 days in the other groups. However, when the TA value did once reach 80, then the survival time of these rabbits was not much greater than in the other groups. The average survival times and amount of tuberculosis at autopsy are shown in table 3.

Attention should be called to one rabbit (No. 56) which died abruptly with relatively little loss in weight only 100 days after infection. It was the only rabbit in all the groups in which the TA value before death was lower than 80, although the last analysis was made 51 days before death. It did not appear sick just before death, which occurred on a very hot day (91°F.). The autopsy revealed no tuberculous lesions except in the lungs, but there was extensive cavitation and caseation in the lungs and pus in the trachea. The stomach was inflamed and the liver congested, and there was evidence of nephritis. It may also be significant that this rabbit alone gave very poor reactions to tuberculin and conspicuously small and poorly indurated Arthus reactions, which never showed necrotic centers, during the sensitization injections with the A protein.

DISCUSSION

It is of interest that sensitization with tuberculin protein fractions is able to cause a rise to a near critical level in the concentration of the polysaccharide component under discussion in the serum, just as occurs spontaneously during the development of the tuberculous process. Thus, if a sensitization treatment has already produced this change in the serum, a superimposed infection may lead to rapid death, as has been observed in previous experiments (4,6). However, the immunizing process, which can apparently be brought about by BCG vaccination, appears to be able to neutralize this change.

It seems clear from these results that a critical level of 80 TA Klett reading for the serum polysaccharide may be of significant prognostic value in the rabbit.

SUMMARY

A substance containing a polysaccharide radical has been found to increase progressively in the serum of rabbits with the development of tuberculosis. In the experiments here described, when the concentration of the substance reached a value of 80 (Klett colorimeter reading) the weight of the rabbit rapidly declined, and death usually occurred after an average of 105 days. This was true regardless of the treatment prior to infection of the rabbit.

Immunization with BCG previous to infection of the rabbits, however, greatly prolonged the period between the time of infection and the time when the serum polysaccharide concentration reached this critical value, and even occasionally allowed a rabbit to lower its polysaccharide concentration.

The polysaccharide concentration could also be increased during a series of sensitizing injections with a particular tuberculin protein (A), the properties of which are described in this paper. Simultaneously severe Arthus reactions were being produced. If the rabbits were infected when this polysaccharide

value was raised, the time to reach the critical value was shortened and death occurred sooner than in the control rabbits.

Sensitization with another protein (C) also did not have an inhibiting effect upon the appearance of the serum polysaccharide during subsequent infection, as was caused by immunization with BCG.

SUMARIO

Significación de las Alteraciones del Contenido de Polisacárido Sérico durante la Sensibilización y durante el Desarrollo de la Tuberculosis

Una sustancia, recién descubierta, que contiene como radical un polisacárido, aumenta gradualmente en el suero sanguíneo de los conejos al irse desarrollando la tuberculosis. En los experimentos aquí descritos, al alcanzar la concentración de la misma una cifra de 80 (lectura con el colorímetro de Klett), el peso del conejo descendió rápidamente y la muerte sobrevino por lo general tras un promedio de 105 días, sucediendo esto independientemente del tratamiento seguido antes de la infección del conejo.

Sin embargo, la inmunización con BCG antes de la infección de los conejos prolongó considerablemente el período de tiempo transcurrido entre la fecha de la infección y la fecha en que la concentración sérica del polisacárido alcanzó dicha cifra crítica, y hasta permitió que de cuando en cuando algún conejo rebajara su concentración de polisacárido.

Pudo también hacerse subir la concentración de polisacárido durante una serie de inyecciones sensibilizantes con una proteína tuberculínica dada (A), cuyas propiedades se describen en este trabajo. Simultáneamente se produjeron intensas reacciones de Arthus. Si se infectaba a los conejos cuando se había elevado la cifra del polisacárido, acortábase el tiempo necesario para alcanzar la cifra crítica y la muerte sobrevenía antes que en los conejos testigos.

La sensibilización con otra proteína (C) tampoco ejerció efecto inhibidor, como el ocasionado por la inmunización con BCG, sobre la aparición del polisacárido sérico durante la infección subsiguiente.

Acknowledgment

Appreciation is expressed to Mrs. Mildred Meekins and Mrs. Mamie Cameron for technical assistance.

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LACK OF SENSITIZATION FOLLOWING REPEATED SKIN TESTS WITH STANDARD TUBERCULIN (PPD-S)[1]

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INTRODUCTION

In connection with a study by Hetherington and Eshleman on certain Negro nursing classes, repeated tuberculin tests have been made by one of us (E.D.) at approximately three-month intervals. These tuberculin tests will be discussed in connection with the possibility of obtaining false positive reactions due to sensitization by repeated tuberculin tests.

It has been shown (1, 2) that very large doses of protein fractions isolated from Old Tuberculin, of the standard purified protein derivative preparation PPD–S, and of many other tuberculin protein fractions, will sensitize rabbits when given repeatedly. The doses used in those studies were approximately 2,000 times as much as were used in human beings for the second skin test, which is the heaviest dose used in routine testing in man. Since the average human being weighs about 25 to 35 times as much as a rabbit, these facts throw little light on human sensitization by routine-testing doses.

The present study yields an unusual amount of information concerning sensitization to multiple skin-testing doses. The nurses were usually given two tuberculin tests with first-dose strength tuberculin and, if found to be negative, two more tests with second-dose strength tuberculin at each test period. One test with PPD–S was given for the nurse's own clinical record and the other, when given, helped in the standardization of various batches of PPD–S to be used in investigations conducted by the Public Health Service. Some nurses who remained negative throughout the study received as many as 22 tests at each dosage level in the course of three years of training.

Since the nurses routinely tested were known to be exposed to infection, it is necessary and at the same time difficult to distinguish changes in sensitivity due to tuberculin tests from changes due to the acquisition of minor infections. The data which are presented below are submitted to statistical examination, and the results of the analysis showed no evidence of an increase in sensitivity due to tuberculin testing, although a small increase (or small decrease) in sensitivity from this cause might pass undetected. In any event, it is certain that such average changes, if they actually existed, were small in relation to the fluctuation in response from test to test, and therefore are almost certain to be clinically unimportant.

[1] From Princeton University, Princeton, New Jersey, and The Henry Phipps Institute, University of Pennsylvania, Philadelphia.

[2] Aided by the Office of Naval Research.

[3] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

TABLE 1

Minor Diameters of PPD Reactions in Millimeters in Nurses of Class I (1941–1944)

DATE OF TEST	SUBJECT NUMBER					
	1	2	3	4	5	6
1941 S	0	0	19	0	0	9
1941 D	16	0	—	13	0	—
1942 M	—	0	—	—	6	—
1942 J	—	15	—	—	—	—
1942 D	13	12	—	—	—	—
1943 M	16	*39*	*53*	*54*	—	*54*
1943 D	*16*	—	—	—	11*	—
1944 M	—	—	—	—	*25*	—
Total number of tests						
First dose	8	11	4	6	9	3
Second dose	6	7	2	4	5	2

S = September; D = December; M = March; J = June

0 = negative reactions; — = no test given.

All numbers represent the sizes of reactions to second-dose PPD-S, except those italicized, which record the size of reactions to the first dose.

* The major diameters were usually slightly less than 20 per cent greater than the minor diameters. The heights were 1 ml. for minor diameters 6 to 9 ml., 2 for 10 to 19, and 3 for 20 and over, except for the cases marked in the table with an asterisk, whose heights were 1 ml. less than that given by this "rule."

TABLE 2

Minor Diameters of PPD Reactions in Millimeters in Nurses of Class II (1942–1945)*

DATE OF TEST	SUBJECT NUMBER																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1942 S	0	7	0	7	0	0	24	16	0	0	49	34	0	17	31	22	0	11	0
1942 D	17	23	[illegible]	6	26	0	*18*	*8*	0	0	*16*	22*	0	*9*	34	22	0	7	—
1943 M	18	23	17	13	*39*	—	16	—	0	8	—	24	—	—	22	24	14	—	20
1943 J	—	*63*	—	—	—	—	—	—	—	0	—	15	*32*	—	—	—	—	—	—
1943 S	15	—	—	—	—	—	*17*	—	*45*	0	—	14	—	—	21	17	—	—	6
1943 D	17	—	14	8	—	—	—	—	—	0	—	—	—	—	*35*	25	17	—	—
1944 M	*36*	—	7	—	—	—	—	—	—	0	—	—	—	—	—	15	9	—	18
1944 J	—	—	—	7	—	—	—	—	—	—	—	*29*	—	—	—	—	13	—	16
1944 S	—	—	18	6	—	—	—	—	—	*32*	—	—	—	—	—	—	—	—	—
1944 D	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7	—	—
1945 M	—	—	*45*	*16*	—	—	—	—	—	—	—	—	—	—	—	13	—	—	—
Total number of tests																			
First dose	9	5	12	12	4	2	7	3	7	11	3	11	7	2	6	12	11	2	8
Second dose	8	5	10	10	3	2	3	1	3	9	1	8	3	1	5	11	10	1	7

S = September; D = December; M = March; J = June

0 = negative reactions; — = no test given.

All numbers represent the sizes of reactions to second-dose PPD-S, except those italicized, which record the size of reactions to the first dose.

* See table 1.

EXPERIMENTAL METHODS

Tests were made on the flexor surface of both arms about two inches below the elbow with 0.1 cc. of PPD–S solution containing 0.00002 mg. for the first doses and 0.005 mg. for the second doses. These doses, in the ratio of 1 to 250, were adopted as standard by the National Tuberculosis Association in 1934. If after 48 hours the tests were negative to the first dose, second doses were injected and reactions again read at 48 hours.

TABLE 3

Minor Diameters of PPD Reactions in Millimeters in Nurses of Class III (1943–1946)*

DATE OF TEST	SUBJECT NUMBER											
	1	2	3	4	5	6	7	8	9	10	11	12
1943 S	0	17	17	13	15	0	26	22	0	22	23	17
1943 D	13	—	*15*	0	0	12	15	30	0	0	15	22
1944 M	11	*39*	*51*	26	24	*63*	*29*	32	*29*	12	28*	—
1944 J	22	—	—	—	23	—	—	*12*	—	16	17	*17*
1944 S	9	—	—	—	0	—	—	—	—	13	12	—
1944 D	13	—	—	7	8	—	—	—	—	7	8	—
1945 M	8	—	—	8	—	—	—	—	—	—	0	—
1945 J	6	—	—	—	—	—	—	—	—	11	7	—
1945 S	6	—	—	7	16	—	—	—	—	13	—	—
1945 D	0	—	—	—	*26*	—	—	—	—	7	0	—
1946 M	—	—	—	12	—	—	—	—	—	—	14	—
1946 J	14	—	—	0	—	—	—	—	—	—	17	—
Total number tests												
First dose	20	4	6	15	14	5	6	7	6	18	22	5
Second dose	16	2	2	14	12	4	4	6	4	20	19	4

S = September; D = December; M = March; J = June.

0 = negative reactions; — = no test given.

All numbers represent the sizes of reactions to second-dose PPD-S, except those italicized, which record the size of reactions to the first dose.

* See table 1.

The reactions were measured by the size of the region of induration (and not by the size of the color reaction). A reaction of less than 5 mm. was classified as negative. The greatest diameter, without regard to direction, the minor diameter (measured at right angles to the greatest diameter), and the height were recorded in millimeters.

Tables 1 to 5, in order to save space, give only the minor diameters of the reactions to PPD-S for the five classes to complete training, since the major diameters were usually less than 20 per cent greater than the minor diameters. The heights were 1, 2, and 3 mm., respectively, for diameters of 6 to 9, 10 to 19, and 20+ mm.

TABLE 4

Minor Diameters of PPD Reactions in Millimeters in Nurses of Class IV (1944–1947)*

DATE OF TEST	SUBJECT NUMBER														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1944 S	0	0	0	0	0	8	13	8	15	14	0	18	0	34	8
1944 D	8	0	0	26	0	6	0	8	26	0	0	0	0	15	0
1945 M	0	0	0	7	6	0	8	13	42	21	0	9	0	0	0
1945 J	*25*	*23*	0	17	7	—	12	14	18	0	0	13	0	—	0
1945 S	—	—	0	11	13	16	12	15	29	11	13	18	0	19	0
1945 D	—	30	6	0	15	25	0	12	15*	21	12	0	—	35	0
1946 M	*42*	43*	11	—	0	*10*	0	—	—	—	31	7	0	43	0
1946 J	—	27	8	—	30	—	—	—	—	—	—	—	—	9	—
1946 S	—	22	0	16	12*	—	6	11	—	17	0	16	0	18	0
1946 D	—	0	—	0	10*	—	0	0	—	30	—	21	—	—	—
1947 M	—	—	—	0	0	—	13	0	—	—	—	21*	—	29	0
1947 J	—	24	—	—	—	—	—	—	—	—	—	—	—	—	—
Total number tests															
First dose	9	19	18	18	21	11	18	18	12	16	15	19	16	17	17
Second dose	5	14	15	14	15	7	14	13	10	13	13	15	14	14	14

S = September; D = December; M = March; J = June.

0 = negative reactions; — = no test given.

All numbers represent the sizes of reactions to second-dose PPD-S, except those italicized, which record the size of reactions to the first dose.

* See table 1.

TABLE 5

Minor Diameters of PPD Reactions in Millimeters in Nurses of Class V (1945–1947)*

DATE OF TEST	SUBJECT NUMBER																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1945 S	12	15	0	0	13	16	17	9	20	0	13	15	15*	*44*	11	0	17
1945 D	27	—	0	7	0	17	24	11	12	11*	7	0	12	—	*8*	14	11*
1946 M	8	—	22	17	21	21	23	11*	—	0	0	17	15	—	—	7	12
1946 J	7	—	0	17	18	6	13	28	—	0	10	7	6	—	—	3	17
1946 S	16	11	16	—	8	17	14	11	—	6	—	16	12	—	—	—	7
1946 D	11*	—	0	—	0	12	20	18	—	12	0	0	16	—	—	12*	0
1947 M	17	22	—	—	—	25	6	16	—	0	13	6	7	—	—	0	0
1947 J	0	—	27	—	—	—	—	18	—	—	—	—	0	*48*	—	—	—
1947 S	—	—	*15*	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total number tests																	
First dose	15	8	16	8	12	14	7	15	4	15	15	13	14	4	4	12	15
Second dose	12	6	11	6	8	10	7	13	2	9	12	12	13	0	2	10	11

S = September; D = December; M = March; J = June.

0 = negative reactions; — = no test given.

All numbers represent the sizes of reactions to second-dose PPD-S, except those italicized, which record the size of reactions to the first dose.

* See table 1.

In each table also is given the total number of tests to both first and second doses received by each nurse during her training course. For each recorded reaction to the first dose (italicized) the nurse would usually have received two tests, but only the reaction to the standard PPD–S is recorded in the tables. Two tests would, however, be listed under total number of reactions to the first dose. For each recorded second-dose reaction, the nurse would usually have received two first-dose tests to which she did not react; and then after 48 hours, two more second-dose tests. In these cases two tests would be counted in the total number of first-dose tests and two more as second-dose tests. In a few instances, a nurse was tested with PPD–S only, as is indicated by a lessened number of total tests.

TABLE 6

Ratios of

Conversions to First Dose during Year (through September)
Number Insensitive to First Dose at Start of Year (September)

YEAR*	CLASS OF NURSES					TOTAL	PER CENT
	I	II	III	IV	V		
1941–1942	0/6					0/6	
1942–1943	6/6	9/19				15/25	60
1943–1944		6/9	7/12			13/21	62
1944–1945			1/5	2/15		3/20	15
1945–1946				1/13	1/16	2/29	7
1946–1947					1/13	1/13	7

* All tests after the second full year are included in the second year (occasional extension of a few months.)

RESULTS

The dimensions of the reaction of each nurse at each time of test were known for the first dose, and for the second dose when there was no reaction to the first dose. In view of the lack of quantitative study of the tuberculin reaction and its variations, it seemed best to analyze these data by a method which used only the relative magnitudes of the different reactions and not, explicitly, their numerical magnitudes, and which treated the responses to the first dose (representing considerable sensitivity) separately from the responses to the second dose. This separation of the two doses, of course, requires justification which will be given below.

Responses to the First Dose

In table 6 may be seen the number of subjects beginning to respond to the first dose as the numerator of a fraction, and the number of subjects not responding to the first dose at the beginning of the year as the denominator. The groups are designated by class and by year from September to September. It will be seen that the rate at which reactions to the first dose were acquired was very great during

the years 1942–1943 and 1943–1944, but does not seem to vary very much from class to class. This is consistent with the available information about living conditions and extent of exposure, which will be discussed later. During these two severe years, approximately 61 per cent of the nurses not reacting to the first dose at the beginning of the year developed a first-dose reaction before the end of the year. During the other years the average was approximately 10 per cent.

Since all exposure was certainly not avoided in the years 1944 to 1947, these results are entirely consistent with the hypothesis that almost all initiations of response to the first dose can be traced to exposure rather than to sensitization by tuberculin.

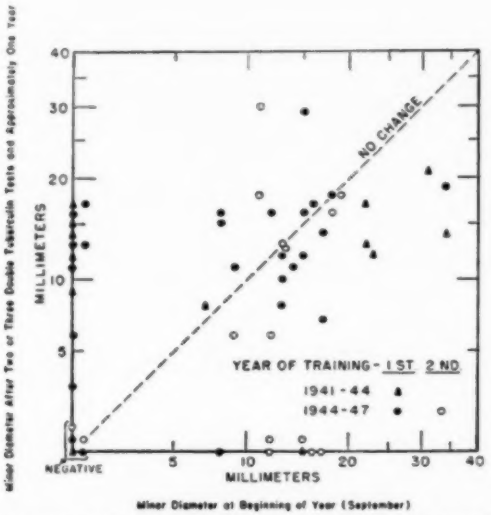

FIG. 1. Change in minor diameter of reaction during one year's training and in two or three intermediate tuberculin tests (excluding cases sensitive to, or becoming sensitive to, first dose).

Quantitative Responses to the Second Dose

Figure 1 shows the responses at the beginning and end of years for all instances in which (a) the nurse was tested in September and did not possess or develop sensitivity to the first dose during the year; or (b), had two or three intermediate tuberculin tests and then a final test. (The year was normally 12 months, although in 7 cases the final test came after 15 months, and in 6 cases after 9 months, since 12-month data were not available.) Only the information as to increases and decreases was used, and is summarized in table 7.

The excess of decreases over increases in the initially positive cases is substantial for 2 of the 3 groups. (For the totals, the excess is statistically significant at the 5 per cent level). Thus a decrease in reaction when the reaction is initially

large is well established. The initially zero cases tended to increase in sensitivity since they could not do otherwise.

This indication is compared with what would be expected from the two possible causes of changes in sensitivity. If the tuberculin tests were gradually building up sensitivity, it would be expected that, on the average, a systematic tendency of reactions to increase would be evident, which does not seem to be at all detectable. If, on the other hand, the sensitivity of the nurses was varying randomly perhaps from miscellaneous causes, conceivably from random infection and random recovery, one would expect a tendency for the lower sensitivity nurses to become, on the average, more sensitive (since they could not become much less sensitive); and for those showing a high sensitivity to become somewhat less sensitive, on the average. This is consistent with what has actually been observed.

TABLE 7

Change on Reaction during One Year

REACTION		NUMBER OF CASES			
Initial	Final	First year of training		Second year 1944–1947	Total
		1941–1944	1944–1947		
zero	positive	5	7	0	12
	zero	1	2	2	5
positive	increased	1	7	2	10
	same	0	1	1	2
	decreased*	6	9	10	25
* Includes decreases to zero as follows		1	1	5	7

It should be noted carefully that random fluctuations in the response of individuals from time to time because of factors which are not recognized, and hence were not controlled or recorded, would have exactly this same effect as would random sensitization and desensitization. Random fluctuation would serve to make a group selected for their low initial reaction tend to contain more people who had momentarily fluctuated downward than upward, and thus, on the average, their sensitivity would be found to increase when they were retested. The only evidence which seems available for distinguishing between these last two causes is provided by the difference between the changes in the years 1942 to 1944 when the conversions to first-dose sensitivity indicate a higher exposure to infection, as compared to those for the years 1944 to 1947. The data suggest but do not prove that the tendency toward decreases in high sensitivity over the year are more pronounced in the years in which exposure to infection was higher. (Since only initially positive cases are available for 1942–1944, the lack of proof is not surprising.) This gives no evidence against the hypotheses that these changes in sensitivity are due either in considerable part to slight infection and gradual recovery or to other random causes.

The following statement[4] from Doctor Hetherington and Miss Eshleman concerning the environment of these nurses is important in connection with the analyses of their tuberculin reactions.

A number of factors, namely, a small decrease in the incidence of tuberculosis in the population from which the patients came, discontinuation of wards for the treatment of known tuberculous patients, a probable decrease in tuberculosis in nonprofessional personnel such as orderlies, etc., and a better standard of housing and economic conditions for the nurses may be an explanation for the reduction in the number of nurses who changed from reactors to the first dose to reactors only to the second dose during the last three years.

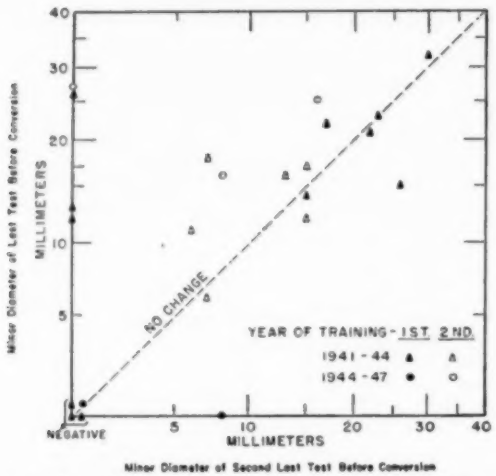

FIG. 2. Last two minor diameters (second dose) before conversion to first-dose sensitivity.

Behavior before Conversion to First Dose

Figure 2 shows the last two reactions with the second dose before a nurse first became sensitive to the first dose; the last plotted against the second last. Data were available for only the 23 cases shown, since many nurses converted to first-dose sensitivity on their second tuberculin test, particularly during the years 1942 to 1944, when exposure to infection was high. Of 8 subjects giving no response on the second test before conversion, 4 gave a positive response on the last test before conversion, and 4 remained zero. Of 15 subjects giving a positive response on the second test before conversion, 9 gave a higher response on the last test before conversion, and 6 a lower response (one dropping to zero reaction).

[4] Further details will be found in the paper to be published by Dr. H. W. Hetherington and Miss Fannie Eshleman.

The tendency to increase in response to the second dose, during the six months preceding conversion to first-dose sensitivity, is small if, indeed, it exists at all.

COMMENT

The observations have now been shown to indicate: (*1*) a predominant influence of living conditions and, presumably, of exposure on the rate at which the nurse became sensitive to the first dose; (*2*) no indication of gradual increase in sensitivity to the second dose among those nurses who did not become sensitive to the first dose; (*3*) no notable tendency to an increase in response just prior to conversion to first-dose sensitivity. These results are all consistent with the picture of sensitization and recovery due to mild infection and the picture of random changes due to other causes, and are inconsistent with a picture of progressing sensitization due to PPD-S.

The failure of any notable tendency for reaction to increase just before conversion justifies the separate analysis of conversion and of changes in reaction to the second dose, since the danger to be guarded against is the possibility that those who are going to convert are also those for whom the reaction before conversion is increasing rapidly. If this were true, and it is clearly not the case in these data, then the analysis of change in second-dose response would have been biased.

SUMMARY

A statistical examination of tuberculin tests made with PPD-S at approximately three-month intervals on five classes of nurses during their three-year training period shows no evidence of an increase in sensitivity due to the tuberculin. Some nurses continued to show no skin reactions even after thirty or more tests.

During the years 1942 to 1944, there were more frequent increases (61 per cent) in sensitivity from the second dose to the first dose than in the years 1944 to 1947 (10 per cent), suggesting a higher rate of infection in the early years.

There was a considerable amount of fluctuation in the degree of sensitivity to the second dose. Fluctuation was also expressed by frequent reversions to negative reactions, often followed by return to positive reactions.

SUMARIO

Falta de Sensibilización consecutivamente a Cutirreacciones Repetidas con Tuberculina Tipo (PPD-S)

Un estudio estadístico de las reacciones a la tuberculina ejecutadas con la preparación PPD-S a plazos aproximados de tres meses en cinco clases de enfermeras durante su período de preparación de tres años, no revela signos de hipersensibilidad debida a la tuberculina. Algunas enfermeras continuaron sin mostrar reacciones cutáneas aun tras 30 o más pruebas.

Durante los años 1942 a 1944, fueron más frecuentes (61 por ciento) los aumentos en sensibilidad de la segunda, comparada con la primera dosis, que

en los años 1944 a 1947 (10 por ciento), indicando así un coeficiente más alto de infección en los primeros años.

La intensidad de la sensibilidad a la segunda dosis fluctuó considerablemente. La fluctuación también se tradujo por frecuentes reversiones a reacciones negativas, seguidas a menudo de retorno a positivas.

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MEASUREMENT OF GROWTH OF TUBERCLE BACILLI BY MEANS OF A SPECTROPHOTOMETER[1,2]

CHARLES HURWITZ AND MILTON SILVERMAN

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INTRODUCTION

Measurement of the amount of growth of tubercle bacilli in liquid media has posed a difficult and tedious problem. Plate counts ordinarily used for determining the number of cells present in a suspension are not readily applicable to tubercle bacilli because of the uncertainty of growth of single cells. Direct microscopic counts are difficult to make because of the clumping of the cells. Consequently, amount of growth has usually been expressed in terms of weight per unit volume (2) or in terms of weight of nitrogen per unit volume of cell suspension (6). Crandall (1) has recently described a direct microscopic method for counting tubercle bacilli in dilute suspension.

The development of a liquid medium containing Tween 80 (3) which results in dispersed growth of tubercle bacilli has made possible an easier method for the determination of the amount of bacterial growth. This method, photoelectric measurements of increased turbidity, has already been used to indicate growth curves of tubercle bacilli in Tween-albumin liquid medium (4, 5). With this method Smith (4) prepared a curve showing the relationship between turbidity of suspension and wet weight of suspended tubercle bacilli. The cells were removed from a solid medium, weighed, ground, and suspended in Tween-albumin liquid medium. An objection to this procedure is that the suspended cells may not have the same state of aggregation, hence the same optical dispersing properties, as cells grown in the medium. Wolinsky and Steenken (5) correlated weight of cells and growth turbidity by deriving a weight factor. The factor was derived by collecting the cells from a known volume of a cell suspension having a known colorimeter reading onto a tared, sintered glass, ultra fine, bacteriologic filter. The cells were washed, dried, and weighed. The dry weight of cells per ml. was then divided by the colorimeter reading to give the factor.

Transmission readings can be accurately made by means of a photoelectric colorimeter, whereas weight measurements of bacterial cells cannot be as accurately determined. If a sufficient number of bacterial weights were determined, their average weight would approach their true weight. Consequently, if a large number of per cent transmissions were graphed as functions of determined bac-

[1] From the Streptomycin Research Laboratory, Laboratory Service of Halloran VA Hospital, Staten Island, New York.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

terial weights, a fitted curve drawn through the points should likewise approach the true correlation. Once the true correlation of per cent transmission and bacterial weight has been established for a given bacterial strain grown in a given medium, the per cent transmission readings, which can be made accurately and easily, could be used to find the bacterial weight. The following data show the relationship between per cent transmission and dry weight of the H37Rv sensitive strain of *M. tuberculosis* grown in Tween-albumin liquid medium.

METHODS

The bacteria were grown at 37°C. in liter flasks containing 250 ml. of Tween-albumin medium at pH 6.9. The medium was inoculated with 0.5 ml. of a 7-day growth of H37Rv strain of *M. tuberculosis* cultured in the same medium. Flasks were removed from the incubator at intervals ranging from four to twenty days. Duplicate per cent transmissions were

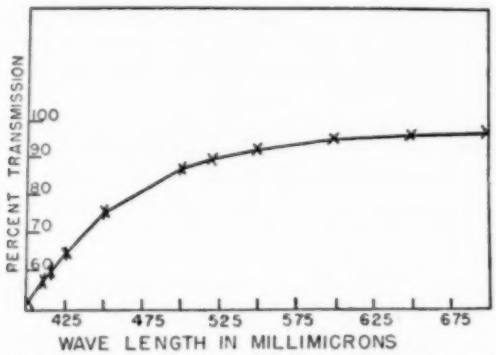

FIG. 1. Absorption curve of tubercle bacilli in Tween-albumin medium

read at 520 millimicrons with a Junior Coleman spectrophotometer, using 19 mm. diameter tubes. The remainder of the bacterial suspension was then centrifuged for five minutes at 2,900 r.p.m. in tared 15 ml. centrifuge tubes in 10 ml. increments, the supernatant being discarded, until 100 to 230 ml. of bacterial suspension had been cleared of bacteria. In this way, the bacterial growth in 100 to 230 ml. of suspension was concentrated in a single tared tube. Ten milliliters of distilled water were added to the packed precipitate which was then broken up and dispersed with a wooden applicator. The suspension was then centrifuged as above. The washing process was repeated three times and the tubes were then dried to constant weight at 60°C. The dry weight of cells, which varied from 2 to 36 mg., was then determined. Fifty-one determinations were made in this manner, and the dry weight of cells, computed to 10 ml. volume, was correlated with the per cent transmission readings.

The following experiment was performed to determine the optimum wave length at which to make the transmission readings.

A 5-day growth of the tubercle bacillus was placed in a spectrophotometer tube and the per cent transmissions were read from 400 to 700 millimicrons. The curve is shown in figure 1. It is apparent that below 500 millimicrons the slope of the curve is too great to be used. Above 500 millimicrons, as the slope decreases, the working range decreases. The wave length of 520 millimicrons was therefore chosen as the optimum compromise at which to determine the per cent transmissions.

RESULTS

The results of the experiments are shown in figure 2, in which per cent transmissions (average value of 2 determinations) were plotted against dry weight of bacteria per 10 ml. The best straight line (unbroken line on graph) and a curved double inflection line (broken) were drawn through the points by visual observation. The relative accuracy of fit of these lines was then determined by

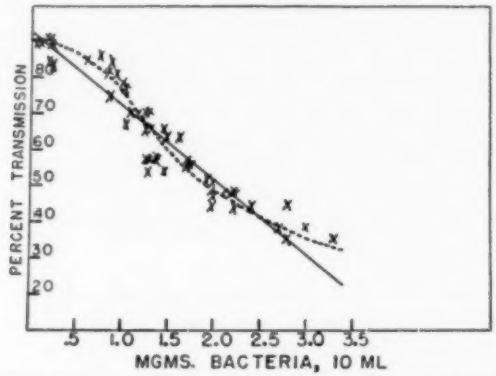

FIG. 2. Per cent transmission as a function of dry weight of bacteria

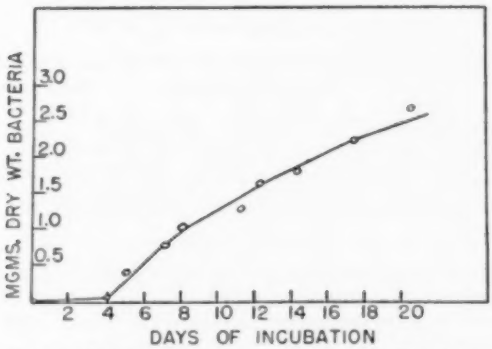

FIG. 3. Growth curve of H37Rv strain in Tween-albumin medium

the method of the least squares, the Δy values being in terms of per cent transmissions. The square root of the $\epsilon\Delta y^2$ variations from the straight line was 37.3 and from the curved line was 29.5. The curved line is therefore a better fit and was adopted.

The probable error (.675 × standard deviation divided by the square root of the number of determinations) was found to be ±0.4 per cent transmission, indicating an expectancy that 50 per cent of the values would fall within that range. This limit of accuracy approaches the accuracy with which the per cent

transmission can be read, indicating that a sufficient number of points have been established to give an accurate curve.

In figure 3, dry weights of cells per 10 ml. of medium were plotted against time to show that the growth curve of the bacteria was well represented.

COMMENT

The method is valuable for determining the rate of growth, total growth, and for standardizing dilute suspensions of tubercle bacilli. Once the curve is established, tedious determinations of dry or wet weights, nitrogen determinations, direct counts of bacterial cells, or the unreliable use of a certain number of days' growth are no longer necessary. The per cent transmission can be quickly and accurately determined and dry weight of cells computed from the curve.

Care must be taken with the transmission readings, since the suspension is not stable. Bubbles, which can lead to inaccurate readings, are easily formed and are hard to dissipate because of the presence of the detergent. In spite of these factors and the tendency of the bacteria to aggregate, the transmission values were surprisingly reproducible.

SUMMARY

A photometric method has been described for the determination of dry weight of tubercle bacilli grown in Tween 80-albumin medium. The method, which has a probable error of ± 0.4 per cent transmission, is applicable to measurements of rate of growth and total growth of tubercle bacilli.

SUMARIO

Medición del Crecimiento de los Bacilos Tuberculosos por medio del Espectrofotómetro

La técnica fotométrica descrita permite determinar el peso en seco de los bacilos tuberculosos cultivados en el medio Tween 80-albúmina. La técnica, que encierra un error probable de 0.4 por ciento en transmisión, tiene aplicación a las mediciones de la velocidad del desarrollo y el desarrollo total de los bacilos.

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EFFECT OF TRITON A-20 AND pH VALUE ON THE STREPTOMYCIN SENSITIVITY OF A RESISTANT STRAIN OF M. TUBERCULOSIS[1,2]

CHARLES HURWITZ AND JOSEPH B. MILLER

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INTRODUCTION

The present investigation has evolved from a study of the use of aerosol streptomycin therapy for pulmonary tuberculosis at Sea View Hospital (9). The aerosol route is employed to gain high local concentration of the drug without the attainment of high concentrations in the blood. It was believed that the effectiveness of streptomycin might be enhanced and the resistance of the bacilli to streptomycin might possibly be overcome by buffering the aerosol to an alkaline pH and adding a wetting agent, Triton A-20.

On this service, an alkaline vehicle is being used in an attempt to overcome the acidity of caseous exudate, since streptomycin activity is decreased in acid and increased in alkaline media. The wetting agent is added because streptomycin is insoluble in lipids, whereas caseous exudate and tubercle bacilli are highly lipid in nature. The streptomycin, wetting agent, and buffer salts are all dissolved in distilled water and administered to the patients as an aerosol. The bacteriologic studies reported in this paper were undertaken to test the value of this combination of agents. The clinical results will be reported in a subsequent publication.

Triton A-20 was first proposed by Dubos and Middlebrook (3) as a surface-active agent for use in liquid media for the growth of tubercle bacilli. It is an aryl alkyl polyether alcohol and is similar to, but less effective than, Tween 80 in promoting dispersion of subsurface growth of tubercle bacilli. It will not hydrolyze to liberate toxic concentrations of oleic acid as does Tween 80. Its clinical advantages for aerosol therapy are low toxicity and extreme stability; it resists hydrolysis by the enzymes of tissue fluids.

A number of reports have shown that Tween 80 enhances the activity of streptomycin. Fisher (4) found that Tween 80 without plasma or albumin in the medium increased the tuberculostatic action of streptomycin in some instances as much as a thousandfold. Plasma or albumin appeared to neutralize this effect to some extent. Williston and Youmans (16) have recently confirmed these results. Other reports have shown that Tween 80 has an enhancing effect on the tuberculostatic activity of certain synthetic organic compounds (18), and that Tween 80 is bacteriostatic for tubercle bacilli (12). No work seems to have been done on the effect of Triton A-20 on the tuberculostatic activity of streptomycin.

[1] From the Laboratory Service of Halloran VA Hospital, Staten Island, New York.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Several investigators have shown that a decrease in pH value decreases the bacteriostatic action of streptomycin. Murray and Finland (10), who worked with gram-negative bacilli, reported a twenty- to eighty-fold reduction in activity of the antibiotic at pH 5.8 as compared with its activity at pH 8.0. Loo and his associates (8) found that the diameter of the zone of inhibition, in the assay of streptomycin by the paper-disc plate method, increased with the initial pH of the agar. Wolinsky and Steenken (17), working with *Staphylococci*, showed that the bacteriostatic effect of streptomycin diminished as the pH value of the medium decreased from 7.7 to 5.2. The greatest loss of activity occurred between pH 6.6 and 5.9. Abraham and Duthie (1) reported similar findings based on their work with *Streptococci*, *Staphylococci*, and gram-negative rods.

Little, if any, work seems to have been done on the effect of pH value on the streptomycin sensitivity of tubercle bacilli, nor could the authors find studies in the literature on the effect of pH values on the sensitivity of a resistant strain of tubercle bacilli to streptomycin. Such an effect appeared especially worthy of being studied since the pH value of empyemata and of caseous material in lung cavities has been reported as being acid and slightly acid, respectively, by Freedlander and French (5) and by Hinshaw, Feldman, and Pfeutze (6).

METHOD

A sensitive and a resistant strain of *M. tuberculosis*[3] were inoculated into a synthetic medium containing four levels of Triton A-20 at 5 initial pH values. The inoculum consisted of 0.1 ml. of a 7-day growth of the stock cultures grown in Tween 80-albumin medium.

The medium was kept as simple as possible for supporting growth. It consisted of the same ingredients used by Williston and Youmans (16) except that Bacto casitone replaced Vegex, Triton A-20 replaced Tween 80, and bovine albumin and glucose were omitted. The medium, containing all ingredients but streptomycin, was prepared so that the concentration of the ingredients would be correct when 4.5 ml. were diluted to 5.0 ml. with distilled water.

Four basic media, containing 0.05 per cent, 0.10 per cent, 0.50 per cent, and 1.0 per cent Triton A-20,[4] were prepared in this way. Portions of each of these media were then adjusted to pH 6.0, 6.5, 7.0, 7.4, and 8.0 by titrating the media with NaOH or HCl. The pH values were determined by means of a Beckman pH meter. The media were then pipetted into 20 by 175 mm. test tubes in 4.5 ml. amounts and autoclaved. Streptomycin dilutions in distilled water were then added aseptically in 0.5 ml. quantities so that each pH and Triton A-20 level combination (table 1) was comprised of a set of tubes containing 0, 1, 10, 100, 500, and 1,000 γ of streptomycin base per ml.

After being inoculated, the tubes were incubated at 37°C. and relative growth was read visually each day for fourteen days. Growth was recorded by means

[3] These strains, derived from the H37Rv strain, were obtained from the Trudeau Research Laboratory, Trudeau, New York, in December 1948 and were maintained in Tween 80-albumin medium (pH 6.9) by weekly transfers. Growth of the sensitive strain in this medium was inhibited by 0.3 γ per ml. of streptomycin, while growth of the resistant strain in the same medium was inhibited by 1,000 γ per ml., but not by 750 γ.

[4] Triton A-20 is a 25 per cent aqueous solution of an aryl alkyl polyether alcohol supplied by Rohm and Haas.

of an arbitrary relative scale reading from 0 to 8. Final pH values were determined after sixteen days of growth by means of a Beckman pH meter.

TABLE 1

Sensitivities of a Resistant Strain of M. tuberculosis as a Function of Triton A-20 Concentration and pH Value
Relative Growth in 14 Days

TRITON A-20 CONCENTRATION	STREPTOMYCIN CONCENTRATION IN MICROGRAMS PER ML.					
	0	1	10	100	500	1,000
Initial pH value 6.0						
per cent						
.05	1	1	1	2	3	3
.10	2	1	4	6	6	4
.50	1	1	2	6	4	2
1.00	0	0	1	4	4	2
Initial pH value 6.5						
.10	8	8	8	4	1	1
.50	4	4	6	4	0	0
1.00	3	3	3	2	1	0
Initial pH value 7.0						
.05	1	1	0	0	0	0
.10	4	3	2	0	0	0
.50	2	2	1	0	0	0
1.00	1	1	1	0	0	0
Initial pH value 7.4						
.10	1	1	0	0	0	0
.50	0	0	0	0	0	0
1.00	0	0	0	0	0	0
Initial pH value 8.0						
.05	0	0	0	0	0	0
.10	0	0	0	0	0	0
.50	0	0	0	0	0	0

RESULTS

The sensitive strain, which was inoculated only into pH values of 6.0, 7.0, and 8.0, in concentrations of 0.05 per cent, 0.1 per cent, and 0.5 per cent Triton A-20, did not grow in the presence of 1 γ or more of streptomycin per ml. in any of the above series, and no growth was observed at pH 8.0 in the tubes containing no streptomycin. The growth at initial pH 6.0 without streptomycin was

slightly better than the growth at initial pH 7.0 without streptomycin. Growth at 0.1 per cent and 0.5 per cent Triton A-20 was also slightly better than at 0.05 per cent concentration. The streptomycin sensitivity of the sensitive strain as determined by this procedure was unchanged from that found using Tween 80-albumin liquid medium.

The results of growth measurements of the resistant strain are recorded in table 1, the relative quantity of growth being described in terms of 0 to 8 arbitrary units. An 8-unit growth in these media was approximately equivalent to an 8- to 10-day growth in Tween 80-albumin liquid medium.

TABLE 2

pH Changes Resulting from Growth of M. tuberculosis in Triton A-20 Media

Final pH Values of Media after Growth

TRITON A-20 CONCENTRATION	INITIAL pH VALUES	STREPTOMYCIN CONCENTRATION IN MICROGRAMS PER ML.					
		0	1	10	100	500	1,000
per cent							
.10	6.0	6.4	6.4	6.8	6.8	6.7	6.6
.50	6.0	6.2	6.2	6.3	6.8	6.5	6.3
1.00	6.0	6.2	6.2	6.2	6.5	6.4	6.3
.10	6.5	7.2	7.2	7.2	6.8	6.6	6.5
.50	6.5	6.9	6.9	7.1	6.8	6.6	6.5
1.00	6.5	6.7	6.7	6.8	6.7	6.6	6.5
.10	7.0	7.1	7.1	7.1	7.0	7.0	6.9
.50	7.0	7.0	7.0	7.0	7.0	7.0	6.9
1.00	7.0	7.0	7.0	7.0	7.0	6.9	6.9
.10	7.4	7.4	7.4	7.4	7.3	7.3	7.3
.50	7.4	7.4	7.4	7.4	7.4	7.3	7.3
1.00	7.4	7.4	7.4	7.4	7.3	7.3	7.3
.10*	8.0	8.2	8.0	8.0	8.0	7.9	7.8
.50*	8.0	8.0	7.8	7.8	7.8	7.7	7.6

* These determinations were made on 4-week-old cultures. All other determinations were made on 16-day-old cultures.

Triton A-20 seemed to have both an enhancing and an inhibitory effect on the growth of the streptomycin-resistant strain of the tubercle bacillus. Below 0.10 per cent concentration, the growth of tubercle bacilli was retarded; at 0.10 per cent concentration, the amount of growth reached a maximum and then decreased as the concentration of Triton A-20 was further increased.

The effects of initial pH values on the growth of the resistant strain were even more interesting. Triton A-20 became more inhibitory at the higher pH values studied. Maximum growth occurred at initial pH 6.5 and decreased at all streptomycin and Triton A-20 levels as the pH increased until only a trace of growth occurred at pH 7.4 and no visible growth occurred at pH 8.0.

The effect of the initial pH values on the streptomycin sensitivity of the resistant strain was also striking. At pH 7.0, the strain appeared to be relatively sensitive to streptomycin since it grew in 10 units but not in 100 units per ml. At pH 6.5, the strain appeared to be relatively resistant since it grew in 1,000 units of streptomycin per ml.; while at pH 6.0, the strain appeared to be "dependent," since optimum growth occurred at 100 to 500 units of streptomycin per ml., and poorest growth at 0, 1, and 10 γ per ml.

The final pH values are recorded in table 2. A remarkably close correlation can be found between the amount of visible growth and the shift of pH toward the alkaline region. Evidently an alkaline by-product of growth, probably ammonia resulting from the deamination of asparagine, was produced in the medium. It is interesting to note, however, that the pH values produced by the greatest amount of growth in initial pH 6.5 tubes approach closely the initial pH values of 7.0 where growth was poor. The effects observed must therefore be on the *initiation* of growth rather than on growth itself.

At the high pH values where no growth was observed, a small but significant decrease in pH occurred as the streptomycin concentration increased. That the streptomycin used had a slightly acid reaction was confirmed by measuring the pH of the streptomycin solution.

DISCUSSION

Perhaps the most interesting finding in the foregoing data is the effect of initial pH of the medium on the sensitivity of the resistant strain to streptomycin. As previously observed, the strain acted like a relatively sensitive, resistant, or "dependent" population, depending on the initial pH value of the medium. At pH 6.5, the bacteria in this medium had the same resistance to streptomycin as was shown in Tween 80-albumin medium at pH 6.9. At pH 7.0 and 7.4, the bacteria evidently became much more sensitive to streptomycin. It should be noted that the growth was much poorer at these pH values than at pH 6.5. Although Smith (14) and Schoenbach and Chandler (13) noted that extent of growth of tubercle bacilli did not affect streptomycin sensitivity in their work, the possibility that the limited growth at pH 7.0 in the present medium affected the sensitivity to streptomycin cannot be discounted since Berkman, Henry, and Housewright (2) and Price and his associates (11) found marked differences in sensitivity to streptomycin when the medium was enriched.

At pH 6.0, the strain appears to be "dependent" on streptomycin since the bacteria grew best in 100 to 500 γ per ml. of the antibiotic. The use of the term "dependence" is probably not justified in describing the results of these experiments since, although growth was less at the lower streptomycin concentrations, growth was not entirely prevented. It is more likely that streptomycin at pH 6.0 enhanced growth by acting as a metabolite since growth increased with streptomycin concentration only at this initial pH value. At the highest concentration used, 1,000 γ per ml., some inhibition probably began to appear.

The effect of pH value on the sensitivity of the organism to streptomycin may be explained by assuming changes in metabolism caused by the differences

in hydrogen ion concentration. It has been shown that streptomycin inhibits oxidation of fumarate and pyruvate by *E. coli* and that the bacteriostatic action of streptomycin is probably exerted through inhibition of the terminal respiration, which apparently involves pyruvate-oxalacetate condensation (15). It is possible that in the pH 7.0 medium the resistant strain of tubercle bacillus developed a metabolic path sensitive to streptomycin, whereas at pH 6.5 its metabolic path was similar to that developed by resistant strains in Tween-albumin medium at pH 6.9. At pH 6.0, the metabolism may have been altered so that streptomycin was utilized as a metabolite.

The effect of pH on the sensitivity of tubercle bacilli becomes of possible clinical importance when one considers the different pH values of the tissues in which tubercle bacilli are found. As previously noted, empyemata have been reported as being acid, and caseous material in cavitations as being slightly acid. Further studies must be made to determine the possible role of the pH of these tissues on the activity of streptomycin on tubercle bacilli situated in these loci.

As reported in the introduction, Tween 80 has also been reported to enhance the activity of streptomycin. The explanation for the enhancing action of Tween 80, namely, the formation of toxic quantities of oleic acid by hydrolysis, cannot be extended to Triton A-20 because the latter detergent is not an oleate, as is Tween 80.

It is more likely that enhancement of activity of streptomycin by these surface-active agents results from the increase in surface area and hence surface activity of the bacilli. According to our results, however, the enhancement of streptomycin activity is found only at the higher pH values studied where Triton A-20 itself was found to be inhibitory. An additive effect of the Triton A-20 on the streptomycin would seem to exist. This additive effect evidently disappears at lower pH values.

It is also noticeable that Triton A-20 is definitely inhibitory to the bacilli at concentrations of 0.5 per cent and 1 per cent, while an enhancing effect on growth was observed as the concentration of Triton A-20 was increased from 0.05 per cent to 0.1 per cent. Attention is also drawn to the increased inhibitory effect of Triton A-20 as the pH increased above 7.0. It is probable that, at the lower levels of Triton A-20 concentration, an increase in concentration of the surface-wetting agent promoted growth by dispersing the cells and thereby increasing surface area and surface activity. As the concentration of detergent increased, however, it is possible that the detergent disoriented the outer lipoprotein bacterial layers which act as a selective semipermeable membrane.

Triton A-20 itself appeared to have no effect on streptomycin sensitivity since an increase in Triton concentration at any pH value resulted in no change in growth in the presence of streptomycin which could not be explained as a result on growth without streptomycin. Thus at pH 6.0, the inhibition of growth at 1.0 per cent Triton A-20 concentration in the presence of 1 γ of streptomycin per ml. is also found in the control tube without streptomycin. The differences found at pH 6.5 and pH 7.0 may be accounted for by the uncertainty of distinguishing a small amount of growth. At pH 7.4, the lack of growth in the

presence of 1 γ of streptomycin per ml. at 0.5 per cent and 1.0 per cent Triton A-20 was paralleled by no growth in the control tubes.

The inhibitory effect on growth of tubercle bacilli by Triton A-20 as its concentration increased remained about the same at each pH value studied. As the pH value increased above 6.5, the sensitivity of the resistant strain of tubercle bacilli to streptomycin increased. It is possible, therefore, that an aerosol solution, buffered at pH 8.0, and containing streptomycin and Triton A-20, might be effective even against resistant strains of tubercle bacilli. Because of the inhibitory effect of Triton A-20 on growth of the tubercle bacilli at pH 8.0, it is also possible that Triton A-20, without streptomycin but buffered at pH 8.0, may have a tuberculostatic effect when given by means of the aerosol route.

SUMMARY

The effect of Triton A-20 concentration and pH on the sensitivity of a resistant strain of *M. tuberculosis* to streptomycin was studied. At an initial pH of 7.0, the tubercle bacillus grew in the presence of 10, but not of 100, γ of streptomycin per ml. of medium. At an initial pH of 6.5, the bacteria grew in as high a concentration as 1,000 γ of streptomycin per ml. At an initial pH of 6.0, the organism grew well in 1,000 units of streptomycin per ml. and displayed optimum growth between 100 and 500 γ of streptomycin per ml.

Triton A-20 had an enhancing effect on growth in lower concentrations and an inhibiting effect in higher concentrations. Optimum growth occurred at 0.10 per cent concentration. Triton A-20 became increasingly inhibitory to the tubercle bacilli as the pH was increased above 7.0. Variations in concentration of Triton A-20 appeared to have no effect on streptomycin sensitivity of tubercle bacilli.

The possible use of an alkaline aerosol solution of Triton A-20, with or without streptomycin, for the treatment of pulmonary tuberculosis is discussed.

SUMARIO

Efecto del Tritón A-20 y de su valor en pH sobre la Sensibilidad a la Estreptomicina de una Cepa Resistente del M. Tuberculosis

Este estudio reza con el efecto de la concentración y del pH del Tritón A-20 sobre la sensibilidad a la estreptomicina de una cepa resistente del *M. tuberculosis*. A un pH inicial de 7.0, el bacilo tuberculoso proliferó en presencia de 10, pero no de 100, microgramos de estreptomicina por ml. de medio. A un pH inicial de 6.5, las bacterias proliferaron hasta a una concentración de 1,000 microgramos de estreptomicina por ml. A un pH inicial de 6.0, el microbio se desarrolló bien en 1,000 unidades de estreptomicina por ml. y mostró desarrollo óptimo a una concentración de entre 100 y 500 microgramos de estreptomicina por ml.

El Tritón A-20 ejerció efecto fortificante sobre el desarrollo a concentraciones bajas e inhibidor a concentraciones altas. El crecimiento óptimo tuvo lugar a concentraciones de 0.10 por ciento. El Tritón A-20 se volvió cada vez más inhibidor para los bacilos tuberculosos a medida que el pH subía de 7.0. Las

variaciones en la concentración del Tritón A-20 no parecieron ejercer efecto sobre la sensibilidad de los bacilos tuberculosos a la estreptomicina.

Discútese el posible empleo de una solución aerosólica alcalina de Tritón A-20, con o sin estreptomicina, para el tratamiento de la tuberculosis pulmonar.

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THE PRESERVATION OF STOCK CULTURES OF MYCOBACTERIUM TUBERCULOSIS BY FREEZING[1,2,3]

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It was deemed advisable to determine whether or not stock cultures of *M. tuberculosis* can be maintained by some means other than monthly transfers. Direct freezing of the culture, either in liquid albumin-Tween medium (1) or on solid glycerinated egg yolk medium (2), was not satisfactory. However, the organisms remain viable if a protective colloid is present.

In these experiments the organisms were grown on solid glycerinated egg yolk medium and were washed off with a sterile 5 per cent solution of bovine serum albumin. The same results were obtained when the organisms were grown on

TABLE 1

A Comparison of the Preservation of Various Cultures of M. tuberculosis at −34°C

CULTURE	MINIMUM NUMBER OF VIABLE CELLS PER ML.				
	Before freezing	Months of storage			
		1 month	4 months	7 months	12 months
BCG	10^6	10^6	10^6	10^4	10^4
TB-1*	10^4	10^4	10^6	10^4	10^4
Ravenal	10^4	10^4	10^4	10^4	10^4

* TB-1 is the number of a stock culture of the Department of Agricultural Bacteriology, University of Wisconsin, Madison.

Dubos liquid medium and centrifuged off before being resuspended in the albumin solution. The suspension of bacilli was then distributed with a syringe and needle into small glass tubes (about 10 by 60 mm.), about 0.5 ml. per tube. These tubes were plugged with cotton and covered with lead foil. The suspension was frozen rapidly by immersing the tubes individually into an ethanol-dry-ice mixture and stored at −34°C. As a safety precaution, the tubes were packed into small glass jars with tight-fitting lids to prevent any possible contamination from a broken or inverted vial should the mechanical freezer fail.

A method of dilution "to extinction" in Dubos liquid albumin-Tween medium was found to be a more satisfactory procedure for estimating numbers of viable cells than the more commonly employed plating technique. Tenfold serial dilu-

[1] From the Department of Agricultural Bacteriology, University of Wisconsin, Madison, Wisconsin.

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[3] Published with the permission of the director of the Wisconsin Agriculture Experiment Station.

tions of the suspension were made in large test tubes, 25 by 150 mm., containing 5 ml. of the medium, and were observed after three weeks' incubation at 37°C. The numbers of viable cells in the suspensions were estimated before freezing and at monthly intervals during the storage period.

A summary of some of the results obtained with three of the cultures, as shown in table 1, indicates that there is no appreciable decrease in numbers of viable cells after twelve months' storage. These cultures are still being carried in the conventional manner so that the virulence and growth characteristics may be compared. Since Steenken (in Waksman's book, *Streptomycin. Its Nature and Practical Application*, Baltimore, The Williams and Wilkins Company, 1949) observed that cultures of *M. tuberculosis* kept in the deep freeze did not lose their streptomycin resistance after twenty-two months, however, it is expected that the virulence and growth characteristics should also remain unchanged.

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COMPARISON OF A LIQUID AND A SOLID MEDIUM METHOD FOR DETECTION OF STREPTOMYCIN-RESISTANT MYCOBACTERIUM TUBERCULOSIS[1,2]

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INTRODUCTION

The emergence of tubercle bacilli resistant to streptomycin in patients treated with this antibiotic is now well known (1, 2, 3, 4, 5). Originally, a liquid medium to which serial dilutions of streptomycin had been added was used to demonstrate this phenomenon *in vitro* (6, 7). Although valuable information has been obtained by this method, it is not a procedure easily adaptable to routine use. For *in vitro* studies it is advisable to obtain cultures at frequent intervals on both smear-positive and smear-negative specimens in order that data may be accumulated for integration with clinical chemotherapeutic studies. At the same time, the demands for cultures for the demonstration of tubercle bacilli in smear-negative concentrates has increased steadily. These two conditions create such a volume of culture work that it is essential to reduce laboratory procedures to a minimum compatible with an efficient laboratory service.

It has been found by Pyle (8) and by Steenken *et al.* (9) that a solid medium to which streptomycin has been added affords a method that can be used to demonstrate streptomycin-resistant tubercle bacilli from primary cultures of sputum. The solid-medium method has several features that make it preferable as a routine procedure and it is the purpose of this paper to present a comparison of the liquid- and solid-medium methods for detecting the presence of streptomycin-resistant strains of *M. tuberculosis*.

METHOD AND MATERIALS

In this laboratory an inspissated egg-yolk-potato-glycerin-malachite green combination (Report of the American Trudeau Society Committee on the Evaluation of Laboratory Procedure (10)) has given excellent results in routine culture work. Also considerable experience has been gained in the determination of the emergence of tubercle bacilli resistant to streptomycin through the use of Dubos Tween-albumin liquid medium (6) to which streptomycin has been added in serial dilutions (2). In the present study, the only change in laboratory procedures was the addition of streptomycin in quantities of 10, 50, and 500 γ per ml. to the solid medium prior to inspissation *at 90°C. for one hour.*

[1] From Veterans Administration Hospital, Sunmount, New York.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

The amount of active and unaltered streptomycin in the inspissated medium has not as yet been satisfactorily determined, although Steenken *et al.* (9), from preliminary studies, suggest that approximately one-third of the streptomycin remains unaltered after inspissation of the medium. On this basis, admittedly inaccurate because of the difficulties of obtaining an accurate chemical assay, and for convenience, the streptomycin content in the different dilutions is considered to be 3.5, 15, and 200 γ per ml. of inspissated medium.

Aliquot portions of the sediment from specimens were flowed over the surface of 5 tubes of the solid medium, 2 without streptomycin and one each that contained 3.5, 15, and 200 γ of streptomycin per ml. of medium. After inoculation the tubes were kept in a slanted position at 37.5°C. for twenty-four hours and then were incubated at 37.5°C. in an upright position for six weeks. Weekly readings and recordings were made from the third through the sixth week. At the end of six weeks a random sample from the growth on one of the non-streptomycin tubes was used to determine the degree of resistance to streptomycin by the liquid-medium method.

One hundred cultures from patients who had never been given streptomycin and 510 cultures from patients during or after a course of streptomycin therapy provide the data for the comparison of the solid- and liquid-medium methods.

TABLE 1

Comparison of Liquid-medium and Solid-medium Methods on 100 Direct Cultures from Sputum from Non-streptomycin Patients

Amount of streptomycin per ml. of Tween-albumin liquid medium necessary to inhibit growth	Cultures with and without streptomycin on solid medium				
	Total	Growth only on Control 0 γ/ml.	Growth on 3.5 γ/ml.	Growth on 15 γ/ml.	Growth on 200 γ/ml.
0.0 to 1.0	87	83	4	0	0
1.0 to 2.5	13	12	1	0	0
Greater than 2.5	0	0	0	0	0
Total	100	95	5	0	0

Seventy-two-hour sputum and fasting gastric contents were diluted with equal parts of 3 per cent sodium hydroxide, homogenized in a converted paint mixer (11) for fifteen minutes and then incubated for thirty minutes in a water bath at 37°C. The specimens were then centrifuged for fifteen minutes at 2,000 r.p.m., the supernatant fluid was decanted, and the sediment was neutralized with 1/N hydrochloric acid with phenol red as an indicator. The sediments were resuspended in sterile normal saline and again centrifuged for fifteen minutes at 2,000 r.p.m. The supernatant fluid was decanted, the sediment thoroughly suspended in sterile normal saline (total volume of 1 ml.) and cultures were made from this suspension. The concentrates from two successive fasting gastric samples were pooled to give material for a single culture.

RESULTS

A comparison of streptomycin sensitivities, determined by solid and liquid media on 100 cultures from patients who had not received streptomycin, is recorded in table 1. There was no growth in the liquid medium that contained concentrations of more than 1 γ of streptomycin per ml. In five instances, a few isolated colonies appeared on the solid medium containing 3.5 γ of streptomycin per ml. when the sample of the same culture was inhibited by 1 γ of streptomycin per ml. of liquid medium. It is of interest that these small numbers of strepto-

mycin-resistant tubercle bacilli were not detected by the liquid titration method. Also, there was no instance of growth in more than 1 γ of streptomycin per ml. of liquid medium when growth was absent on the solid medium that contained streptomycin.

A comparison of the results obtained on solid and in liquid medium on 510 cultures obtained from patients during or after streptomycin therapy is presented in table 2. There were 217 cultures that were inhibited by less than 5 γ of streptomycin per ml. of liquid medium. Of these, 144 (68 per cent) revealed abundant growth on the solid medium without streptomycin, whereas abundant growth occurred in but one instance (0.7 per cent) on the streptomycin-containing tubes, that being on the 3.5 γ tube. One hundred twenty-two cultures grew in 1,000 γ of

TABLE 2

Comparison of Liquid- and Solid-medium Method on 510 Cultures Obtained from Direct Planting of Sputum Concentrates from Patients during or after Streptomycin Therapy

MICROGRAMS OF STREPTOMYCIN PER ML. OF LIQUID MEDIUM IN WHICH GROWTH OCCURS	DENSITY AND DISTRIBUTION OF GROWTH ON SOLID MEDIUM WITH AND WITHOUT STREPTOMYCIN ADDED															
	No streptomycin				3.5 γ streptomycin/ml.				15 γ streptomycin/ml.				200 γ streptomycin/ml.			
	Total Culture	1+ or More	10 to 50 Colonies	<10 Colonies	Total Culture	1+ or More	10 to 50 Colonies	<10 Colonies	Total Culture	1+ or More	10 to 50 Colonies	<10 Colonies	Total Culture	1+ or More	10 to 50 Colonies	<10 Colonies
Up to 5	217	144	35	38	35	1	12	22	1	—	1	—	1	—	—	1
Up to 15	93	77	10	6	82	51	21	10	54	13	18	23	20	1	7	12
Up to 1,000	78	69	4	5	76	63	11	2	75	50	21	4	49	7	25	17
Over 1,000	122	108	9	5	119	107	7	5	119	103	11	5	120	99	10	11
Total culture	510	398	58	54	312	222	51	39	249	166	51	32	190	107	42	41

NOTE: Results on solid medium are from direct readings. Those in liquid-medium method are obtained from random samples of growth on non-streptomycin tubes of solid medium.

streptomycin per ml. of liquid medium. Of these, 108 (88 per cent) revealed abundant growth on the *solid medium* without streptomycin, whereas abundant growth occurred in 99 (91 per cent) in all tubes, including the tube containing 200 γ of streptomycin per ml. It is evident that there is close agreement between the two methods in those instances where cultures were either sensitive or resistant to streptomycin. It was also noted that, when growth in 1,000 γ of streptomycin per ml. of liquid medium was obtained from those primary cultures which showed 50 or less colonies on the culture tubes of solid medium without streptomycin, all showed growth on the solid medium containing 200 γ of streptomycin per ml., usually with as many colonies as in the control tube.

Among the cultures (table 2) which were inhibited by 5 or less γ of streptomycin per ml. in liquid medium, 35 (16 per cent) showed growth on solid medium containing 3.5 γ of streptomycin. This is in contrast to the data shown in table 1 where only 5 per cent exhibited growth on the solid medium containing 3.5 γ of

streptomycin, and indicates that some change, although not striking, had occurred in the bacterial population subsequent to the institution of streptomycin therapy.

There is considerably less agreement between the liquid- and solid-medium methods in those instances where titration in liquid medium showed growth between 5 and 1,000 γ of streptomycin per ml. Of the 93 cultures in which there was growth in 5 and no growth in 15 γ of streptomycin per ml. in the liquid medium, 77 (82 per cent) showed abundant growth on the control tube of solid medium. Of these 77 cultures, 50 (66 per cent) showed abundant growth on the 3.5; 13 (17 per cent), on the 15; and one (1.4 per cent) on the 200 γ tube. A similar discrepancy between the two methods is apparent in those cultures which in liquid medium grew in more than 15 but not in 1,000 γ of streptomycin per ml. These discrepancies conceivably may be due to the random sample of the primary growth that was used in the liquid titration method. It has been noted in this laboratory that somewhat inconsistent results have been obtained by the liquid-medium method in demonstrating the resistance of the bacterial population in concentrations between 5 and 1,000 γ of streptomycin. This suggests that the solid medium is the more accurate method of determining the relative proportion as well as the relative degree of resistance in the bacterial population.

In 10 per cent of the primary cultures on solid medium, only a few colonies (less than 20) were present on the control tubes. In these instances an accurate estimation of the sensitivity of the culture could not be determined directly. In those instances in which few organisms are present in the concentrate there is a chance that the few colonies which grow may not represent the actual condition of the bacterial population as a whole. Also, there is a possibility that the few organisms present may have been planted on only one tube of the series. For these reasons it is advisable to determine the sensitivity of the growth which is obtained, and this can be done by triturating a representative sample of the growth in either a small amount of Tween-albumin medium or saline containing Tween; and by planting 0.1 ml. of the suspension on a series of control and streptomycin-containing tubes of solid medium.

DISCUSSION

The data on the solid-medium method were derived from the results obtained from the planting of aliquot portions of concentrated specimens. The data on the liquid-medium method were derived from random samples of growth taken from the solid-medium tubes without streptomycin. There were then two random samples of a bacterial population to be compared. A comparison of the results of these random samples indicated that there was close agreement between the liquid- and solid-medium methods if the bacterial population was in large part either sensitive or resistant to streptomycin. However, if the bacterial population was composed of a mixture of sensitive and resistant organisms, a discrepancy of 30 per cent was found between the two methods. In these instances the solid-medium method appeared to be preferable since it disclosed the relative proportions of the bacterial population which grew in the presence of different con-

centrations of streptomycin, and it may be that the random samples used in the liquid-medium method did not represent accurately the bacterial population as a whole. It was apparent throughout the study that the significant advantages of the solid-medium method were the simplicity of operation and the determination of the proportion of the bacterial population which was resistant to streptomycin, as well as the relative degree of resistance from cultures derived directly from concentrates of specimens. In this study sufficient growth occurred in 90 per cent of the primary cultures on solid medium so that no further testing was necessary to determine streptomycin resistance.

It has been shown that the addition of less than 1 per cent of tubercle bacilli resistant to 1,000 γ of streptomycin per ml. of liquid medium to a streptomycin-sensitive bacterial population yielded good growth in concentrations of 1,000 γ per ml. (12). In this study it was found that on primary isolations the presence of a few colonies on the 200 γ of streptomycin tube with abundant growth on the control tube failed to yield growth in a concentration of 1,000 γ of streptomycin in the liquid medium from the random sample taken from the control tube. It would seem probable that in these instances the sample tested failed to contain the resistant organisms.

The solid-medium method used may be criticized because the amount of active and unaltered streptomycin in the inspissated medium is not accurately known. Despite this fault, it appears that this method is preferable to the liquid-medium method as a routine procedure because it shows results on direct inoculation from specimens that compare favorably with results obtained by subculture in the liquid-medium method wherein exact amounts of streptomycin are known. It has been our experience with the liquid-medium method that emergence of a predominantly resistant bacterial population frequently occurs in a relatively short time in a patient treated with streptomycin, and that resistance to a concentration of 1,000 or more γ of streptomycin per ml. soon is in evidence. This same phenomenon has been noted with the solid-medium method wherein weekly cultures of sputum concentrates were made from patients during streptomycin therapy. Aside from the simplicity of operation in a routine program, it is advantageous to determine from direct culture of specimens the quantitative and qualitative changes in the bacterial population that are evidenced during or after a course of streptomycin therapy, and to be freed in large part from the testing of subcultures. The three different quantities of streptomycin used in the solid-medium method appear to give a sufficient range of concentrations for practical purposes.

With the liquid-medium method, the relative degree of resistance to streptomycin of a random sample of a culture is determined. With the solid-medium method the amount of growth, the proportion of the growth that is resistant to streptomycin, and the relative degree of this resistance is determined directly from a random specimen from a patient. Therefore, it is not possible to use the same method of reporting the results obtained by the two tests. In the laboratory at Sunmount the form shown in table 3 has been found to be a convenient way to record the results obtained from the direct planting of a specimen on solid

medium with and without streptomycin incorporated, and this report is inserted into the patient's record. By consulting serial reports on any given patient, the clinician can detect easily any changes which have occurred in the bacterial population of the random samples that have been tested. The laboratory interpretation of each test relative to sensitivity or resistance to streptomycin is based upon the last recorded observation and is given under results in table 3.

The following are the terms used and their meaning:

1. *Sensitive*—A marked disparity between the amount of growth on the control and streptomycin tubes

2. *Slightly resistant*—Comparable growth on the control and the 3.5 γ streptomycin tube, with marked disparity of growth on tubes containing higher concentrations of streptomycin

TABLE 3

Form Used to Report Laboratory Test for Streptomycin Sensitivity

(Interpretation is based on last reading of culture)

Streptomycin Sensitivity Tests on Solid Medium

SOLID MEDIUM WITH STREPTOMYCIN	CONCENTRATED STREPTOMYCIN	DAYS OF INCUBATION			
		18	25	32	39
	γ/*ml.*				
Case No. 13 675	0	2+	3+	3+	4+
Spec.: Sputum	3.5	1+	1+	1+	2+
Date of culture:	15	0	10	45	1+
July 9, 1948	200	0	0	4	10

Results: Strain "moderately resistant" to streptomycin.

Growth is observed periodically for six weeks.

4+ Growth completely confluent.

3+ Growth not quite confluent.

2+ More than 100 colonies but less than 3+.

1+ For about 50 to 100 colonies.

Actual colony count if less than 50.

3. *Moderately resistant*—Comparable growth through the 15 γ streptomycin tube, with marked disparity of growth on the 200 γ streptomycin tube

4. *Resistant*—Comparable growth on all tubes.

SUMMARY

A comparison is presented of the Dubos Tween-albumin serial dilution of streptomycin technique with an inspissated solid medium in which streptomycin is incorporated. A close agreement between the two methods was found in those instances in which the bacterial population as a whole was either sensitive or resistant to streptomycin. There was a discrepancy in 30 per cent of instances in which the liquid-medium technique revealed good growth in concentrations of more than 5 but less than 1,000 γ of streptomycin per ml. In these instances it appears that the solid-medium method is preferable in that it indicates the relative proportion of the bacterial population from direct inoculation of specimens which is resistant to streptomycin as well as the degree of resistance. The

random samples from primary growth on the control tubes used in the liquid-medium method may not be representative of the population unless the population as a whole is either sensitive or resistant to streptomycin.

Incorporation of different concentrations of streptomycin in an inspissated egg yolk-potato-glycerine-malachite green medium affords a practical routine method for determining the resistance of *M. tuberculosis* to this drug from the growth obtained directly from concentrates of sputum and other specimens.

A method of reporting *in vitro* resistance studies on individual cultures is presented. Qualitative and quantitative changes in random samples of the bacterial population are easily detected from cultures of concentrates of specimens from a patient during or after streptomycin therapy. It is believed that retesting by subculture is not necessary provided a growth of more than 20 colonies is present on the culture medium which contains no streptomycin.

SUMARIO

Comparación de las Técnicas de Medio Líquido y Sólido para el Descubrimiento del Mycobacterium Tuberculosis Estreptomicinorresistente

Comparan con el mayor detenimiento en este trabajo las AA. la técnica de dilución seriada de estreptomicina en el medio de albúmina-Tween de Dubos con la del medio sólido espesado al cual se agrega estreptomicina. Encontróse mucho acuerdo entre las dos técnicas en los casos en que la población bacteriana era en conjunto ya sensible o resistente a la estreptomicina. Hubo discrepancia en 3° por ciento de los casos en que la técnica del medio líquido revelaba buenas colonias a concentraciones de más de 5 pero menos de 1,000 γ de estreptomicina por ml. En esos casos, parece que la técnica del medio sólido es preferible por indicar, por la inoculación directa de los ejemplares, la relativa proporción de población bacteriana estreptomicinorresistente e igualmente el grado de resistencia. Las muestras tomadas al azar de las colonias primarias en los tubos de control usados en la técnica del medio líquido acaso no sean típicas de la flora, a menos que ésta sea en conjunto ya sensible o resistente a la estreptomicina.

La incorporación de diversas concentraciones de estreptomicina en el medio sólido espasado aquí mencionado ofrece un método práctico para determinar la resistencia del *Mycobacterium tuberculosis* a dicho antibiótico por las colonias obtenidas directamente de los concentrados de esputo y otros ejemplares.

Preséntase un método para comunicar los estudios de la resistencia *in vitro* de cultivos dados. Es fácil distinguir las alteraciones cualitativas y cuantitativas en las muestras tomadas al azar de la población bacteriana, por los cultivos de ejemplares concentrados obtenidos de un enfermo durante la estreptomicinoterapia o después de la misma. La recomprobación con subcultivos no resulta necesaria con tal que haya más de 20 colonias presentes en el medio de cultivo que no contiene estreptomicina.

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Case Reports

SOME PELVIC COMPLICATIONS OF PNEUMOPERITONEUM

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During the induction and early maintenance of pneumoperitoneum for the treatment of pulmonary tuberculosis, patients may experience a variety of discomforts. Included among these are: soreness of the shoulders due to diaphragmatic irritation by air, rolling and bubbling of air with change of posture, arresting pain when altered position of the body causes air to pocket between the liver and diaphragm, and soreness of the muscles or soft tissues subcostally when such structures are stretched by the air under pressure (1, 2). The patients soon learn to avoid the positions which cause pain, and within approximately five to six weeks (3) the above symptoms either disappear or lessen sufficiently in severity to be tolerable.

When these discomforts are not alleviated or when they increase in severity, complications of the pneumoperitoneum should be suspected.

One group of complications of pneumoperitoneum is characterized (a) by an underlying weakness or defect in the structures bounding the peritoneal cavity, either congenital or traumatic; and (b) by these defects being aggravated or made apparent because of the increased abdominal pressure associated with the pneumoperitoneum. Among these are hernias, pneumoceles, rupture of the diaphragm, and some instances of mediastinal emphysema, with or without associated pneumothorax (4, 5, 6).

The purpose of this report is to present some pelvic complications of pneumoperitoneum which, to our knowledge, have not previously been reported.

CASE REPORTS

Case 1. F. F., a 57-year-old white woman, was found to have active, bilateral, moderately advanced pulmonary tuberculosis in October 1948. Her past history included two uncomplicated pregnancies terminating in normal labor and delivery, thirty-one and thirty-five years previously. Ten years before admission the patient was sterilized by deep X-ray irradiation because of uncontrollable uterine bleeding. On physical examination positive findings were limited to the chest, and the pelvic and rectal examinations revealed no abnormalities. Pneumoperitoneum was initiated on January 19, 1949. The patient had discomfort from the start, necessitating smaller and less frequent refills as time progressed. The abdominal distress gradually increased in severity. Then, a sensation of lower abdominal pressure and a crampy perineal pain developed. Pelvic examination showed a moderate degree of cystocele and rectocele. After a Hodge pessary was inserted, the pains disappeared in spite of continuation of the pneumoperitoneum.

Perineal pain recurred six months later when, against advice, the patient began doing heavy housework. Because of the persisting distress the patient finally discontinued the pneumoperitoneum. Following this, no further pelvic pain was experienced. The cystocele and rectocele were greatly improved; the pessary was no longer required.

Case 2. M. S., a 25-year-old white woman, was found to have active, moderately advanced pulmonary tuberculosis in March 1948. Five years before she had had a normal full-term

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pregnancy with subsequent brief labor of three and one-half hours' duration terminating in a spontaneous delivery. The child weighed four pounds, nine and one-half ounces at birth. Pelvic findings several weeks post partum revealed no abnormalities. No weaknesses in the perineal tissues were noted; the uterus was normal in size and position. Subsequent periodic pelvic examinations were negative except for the finding on one occasion of a trichomonas vaginitis. The patient stated that she had had occasional dysmenorrhea and leukorrhea since the birth of her child. Except for a few scattered rales heard over both sides of the chest, the physical examination was entirely negative.

A pneumoperitoneum was started on April 22, 1948. It was maintained, relatively symptom-free, with refills from 750 to 900 cc. weekly. Intra-abdominal pressures ranged from +6, +8 to +9, +11 cm. of water.

On April 20, 1949 the patient noted a feeling of heaviness in the perineal region and complained of lower abdominal crampy pain, with burning and frequency of urination. She stated that she felt a mass protruding from her vagina. Examination revealed a first degree prolapse of the uterus, a tender inflamed cervix, and a marked degree of cystocele and rectocele. With chemotherapy and bed rest, the urinary symptoms abated and the cervicitis improved. The crampy pains disappeared when the uterus was supported by a Hodge pessary. Three days later they recurred when the pessary "slipped," but vanished again when it was replaced.

In September 1949 the patient experienced painful menstruation. Gynecologic investigation showed tenderness and induration in the adnexa. No specific infection was demonstrated. The patient returned to her gynecologist who treated successfully the nonspecific salpingitis with antibiotics and diathermy. Since then, pneumoperitoneum has been maintained and the patient has been asymptomatic.

COMMENT

The first patient presented a moderate degree of cystocele and rectocele which became apparent after initiation of the pneumoperitoneum. The associated perineal pain was so severe that the size of refills was necessarily limited and hence inadequate. Abandonment of the pneumoperitoneum was considered. Then, the genital relaxations were recognized and the symptoms controlled by means of a pessary. It was important to continue the pneumoperitoneum in view of the bilateral active pulmonary tuberculosis. When the pneumoperitoneum was abandoned later for the reasons mentioned above, pelvic symptoms disappeared, emphasizing the causal relationship between these symptoms and the pneumoperitoneum. Previously, these symptoms had been controlled by the use of a pessary, suggesting that they were secondary to the pelvic defects. It seems reasonable to assume that the cystocele and rectocele were aggravated by the pneumoperitoneum, particularly since they improved so much when the pneumoperitoneum was abandoned.

In the second patient, the pneumoperitoneum had been employed one year before the pelvic complications appeared. It is probably not fair to state that the pneumoperitoneum was the principal factor that caused the cystocele and rectocele and descensus of the uterus. Novak (7) feels that cystocele and rectocele result from congenital or traumatic defects in the fascial supports of the bladder and rectum. However, the pneumoperitoneum with its accompanying increased intra-abdominal pressure was certainly an aggravating factor in their appearance. Fortunately, a pessary controlled the symptoms resulting from the pelvic relaxations. The pneumoperitoneum was continued with slightly smaller refills and the patient has since shown satisfactory progress.

Recognition of these pelvic complications and their temporary treatment with pessaries may allow such patients to continue their pneumoperitoneum therapy when it might otherwise have to be abandoned prematurely. Later, with general improvement, it might be possible to carry out definitive surgical correction of the pelvic abnormalities or to substitute other collapse procedures for the pneumoperitoneum.

SUMMARY

1. Two cases have been presented illustrating pelvic complications of pneumoperitoneum, namely, cystocele, rectocele, and descensus of the uterus.

2. Treatment of these disturbances by the use of pessaries and by decreased frequency or size of refills afforded sufficient relief to permit continuation of the pneumoperitoneum.

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ERYTHEMA NODOSUM WITH TUBERCULIN-NEUTRALIZING SERUM[1]

A Report of Two Cases

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Erythema nodosum has been reported in association with tuberculosis, streptococcal infections and rheumatic fever, coccidioidomycosis, drug sensitivity, and numerous other conditions (1), the significance of the associations being variously interpreted.

The not infrequent concomitance of enlarged hilar lymph nodes (1, 2) has given rise to the claim that some cases may be associated with sarcoidosis, especially where the tuberculin reaction has been negative. In the European literature (3–6) there have been reports of cases of erythema nodosum with hilar lymphadenopathy and negative tuberculin tests said to be related to sarcoidosis. In some instances the diagnosis of sarcoidosis was inferred on strongly suggestive clinical grounds such as development of a uveoparotid syndrome (3, 4), and in a few cases was verified histologically (3, 4, 5) or by positive Kveim test with histologic examination (6).

In the present experience with two cases of tuberculin-negative erythema nodosum with hilar lymphadenopathy, it was impossible either to substantiate or to exclude the diagnosis of sarcoidosis.

The sera of these two patients were tested for tuberculin-neutralizing properties, in view of previous observations (7, 8, 9) that sera from patients with sarcoidosis can destroy the power of tuberculin to produce a typical reaction in the skin of known hypersensitive subjects. This phenomenon, which has been attributed to so-called "anticutins" in serum, may be related to the tuberculin anergy of sarcoidosis (10, 11). Recently Wells and Wylie (9) found the tuberculin-neutralizing power to be present exclusively in the electrophoretically separated gamma-globulin of serum from a patient with sarcoidosis, while none was demonstrable in normal human gamma-globulin. These workers do not consider the neutralization of tuberculin by serum confined to cases of sarcoidosis.

CASE REPORTS

K. M., a 22-year-old female, entered the hospital presenting erythema nodosum lesions over the shins which had been present for three weeks, with stiffness, pain, and swelling of the knees and ankles. For two months the patient had had a cough, which in the last three weeks had been productive of small amounts of yellowish sputum. Roentgenographic examination of the chest showed bilateral hilar lymph node enlargement (figure 1). Films of hands and feet were negative. Plasma proteins were normal (Howe fractionation), but electrophoretic analysis revealed some diminution of albumin and elevation of alpha-2- and gamma-globulins. Nose, throat, and sputum cultures showed no pathogenic bacteria. Electrocardiogram was normal. Tests of cutaneous hypersensitivity to tuberculin with progressively increasing strengths revealed no reaction whatever even with undiluted Old Tuberculin. Kveim test was negative. No peripheral lymph nodes were suitable for biopsy. The erythema nodosum lesions disappeared after a week's bed rest. Four subsequent chest roentgenograms over the ensuing four months revealed the enlarged hilar nodes to be still present, but a film nine months after the onset showed complete regression of the lymphadenopathy.

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D. W., a 29-year-old male, entered the hospital because of painful ankles, elbows, and joints of the hands for three weeks. The symptoms began four days after an upper respiratory tract infection, with sore throat. Two weeks after the onset, erythema nodosum lesions appeared over the legs, and the patient ran a low-grade fever. Roentgenographic examination of the chest revealed bilateral hilar lymph node enlargement (figure 2). Films of hands and feet were negative. Plasma proteins were normal (Howe fractionation), but electrophoretic analysis revealed some diminution of albumin and elevation of alpha-2-globulin.Nose and throat cultures showed no pathogenic bacteria. Electrocardiograms were within normal limits. Tests of cutaneous hypersensitivity to tuberculin with progressively increasing strengths revealed no reaction whatever even with undiluted Old Tuber-

FIG. 1. Patient K. M. Note hilar lymphadenopathy

culin. After three weeks' bed rest the erythema nodosum lesions, joint pains, and fever subsided. No peripheral lymph nodes were suitable for biopsy. After discharge, the patient did not return for Kveim test or further roentgenographic examinations of the chest.

OBSERVATIONS AND DISCUSSION

Serum from each of the 2 patients was mixed with O. T., so that the final dilution was 1:10,000, according to the procedure of Wells and Wylie (9). The mixture was injected intradermally into one arm of known tuberculin reactors (healthy physicians with negative chest microfilms), and into the other arm was injected 1:10,000 O. T. in saline, as a control.

The tests were interpreted as indicating the presence of tuberculin-neutralizing properties in the sera of both K. M. and D. W. In each series of experiments, four of the

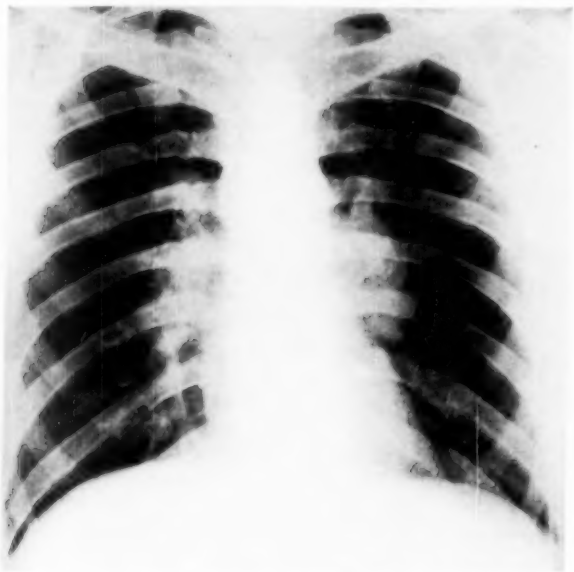

FIG. 2. Patient D. W. Note hilar lymphadenopathy

FIG. 3. Demonstration of tuberculin-neutralizing property of serum. The right arm shows a positive tuberculin reaction to 1:10,000 O.T. injected 48 hours previously. The left arm shows a faint trace of erythema at the site of injection of O. T. diluted to 1:10,000 with serum from patient D. W.

five known reactors exhibited erythema and induration forty-eight hours after the control tuberculin injection, but no reaction or a trace at the site of injection of the tuberculin-serum mixture. Figure 3 illustrates such a result. In each series of experiments, however, a fifth known reactor exhibited erythema with induration on both arms, possibly

representing a sensitivity to the serum, but in any event not invalidating the results above (7, 9).

Normal human serum has been shown not to neutralize tuberculin (7), or to do so infrequently and irregularly (8, 9). As a further control, two additional cases of erythema nodosum were studied. These individuals had normal chest films, and did react to tuberculin in the higher strengths. In one case, erythema nodosum of a week's duration followed an upper respiratory tract infection, and in the other, several episodes of erythema nodosum occurred during chronic nonspecific ulcerative colitis. As expected the sera of these two patients showed no tuberculin-neutralizing activity whatever.

The experiments described cannot in any sense be interpreted as indicating that the erythema nodosum cases with hilar lymphadenopathy necessarily had associated sarcoidosis. The results are recorded merely to call attention to an unexplained phenomenon in a peculiar clinical syndrome which merits further investigation.

SUMMARY

1. Two cases of erythema nodosum with hilar lymphadenopathy and polyarthritis are described.

2. In both patients, tests revealed no reaction to intradermal tuberculin in any strength, including undiluted Old Tuberculin.

3. The sera of these two patients exhibited tuberculin-neutralizing properties.

SUMARIO

Propiedades Tuberculino-Neutralizantes de los Sueros de Casos de Eritema Nudoso Tuberculino-Negativo

1. Descríbense 2 casos de eritema nudoso con linfadenopatía hiliar y poliartritis.

2. Ni uno ni otro revelaron reacción alguna a la tuberculina por vía intradérmica a ninguna concentración, incluso tuberculina antigua sin diluir.

3. Los sueros de esos enfermos mostraron propiedades tuberculino-neutralizantes.

Acknowledgment

The author is indebted to Dr. Walter S. Thompson for cooperation in both the experimental and clinical work.

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SPONTANEOUS PNEUMOTHORAX FOLLOWING PNEUMONECTOMY

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(Received for publication March 3, 1950)

CASE REPORT

W. S., a 43-year-old white male, had pulmonary tuberculosis complicated by a bronchiectasis of the left lung. In the preoperative physical examination, a cardiac arrythmia was noted, but the patient did not give any history of heart trouble. The routine preoperative electrocardiogram was reported as follows: "This electrocardiogram is abnormal, with changes suggesting an extra cardiac source of right heart strain." The heart was shifted into the left chest, as depicted on the chest roentgenogram. This was due to partial atelectasis, as well as fibrosis and retraction of the left lung. The cardiac displacement was thought to explain the abnormal appearance of the electrocardiogram. In order to recheck the history obtained, however, the patient was again quizzed as to whether he had previously suffered with heart disease, and he again denied having any cardiac difficulty. A left pneumonectomy was performed. Auricular flutter developed in the immediate postoperative period and this was converted to auricular fibrillation. He was treated with digitalis and quinidine. A normal rhythm was not apparent again until nine days following surgery. It was quite disconcerting to have the patient admit at this time that he had previously suffered from heart disease, and for a time had taken digitalis. He stated that his concealment of the heart disease was deliberate, for fear his operation might be cancelled. He stated he fully realized the additional risk of the operation in view of his heart disease, but he considered it worth the risk in view of the chance it offered to get well. After return to normal cardiac rhythm, his condition gradually improved. It was necessary to continue intranasal oxygen for three weeks.

Sixty days from the date of surgery, he suddenly became very dyspneic. The dyspnea was not associated with any pain. The diagnostic possibilities lay between spontaneous pneumothorax or partial atelectasis. A bronchoscopy revealed the left bronchial stump to be well healed, and the right tracheobronchial tree to be free of obstruction or mucus. The diagnosis of spontaneous pneumothorax was established by the finding of free pleural space with exploratory needle puncture. Due to technical difficulties, it was impossible to obtain a chest roentgenogram at this time. Eighteen hundred cubic centimeters of air were removed from the pleural space at the first aspiration. This led to temporary relief of his dyspnea. Fifteen minutes later it was necessary to remove 2,500 cc. of air to alleviate his dyspnea. It was obvious that something other than repeated chest aspirations would be necessary in order to overcome the tension pneumothorax. An intercostal catheter (#12 French) was placed in the sixth right intercostal space and connected to a Stedman pump. The suction apparatus was arranged with a water trap, and suction was maintained at 15 cm. of water. This relieved the dyspnea, and respiration was returned to 20 per minute. Breath sounds were heard over most of the right chest except at the extreme apex. For three days the suction was continued, and then an attempt was made to use under-water sealed drainage as a substitute. The dyspnea recurred, and it was necessary to return to the original suction arrangement. It was necessary to insert a second catheter in the right third anterior interspace when the original catheter became completely plugged. The patient continued to have some dyspnea, despite the fact that he was receiving oxygen continuously via nasal catheter. The day following insertion of the second catheter and five days after the onset of the spontaneous pneumothorax, examination revealed that the right lower lobe was aerating poorly. A Pezzar catheter (#24 French) was placed through the ninth intercostal space posteriorly, in order to better evacuate this basilar air. When the second catheter was connected, it was found that one Stedman pump would not remove the air quickly enough. Two Stedman pumps were therefore connected in tandem, and this

arrangement accomplished the desired result. The two pumps in tandem were continued through the tenth day, and all suction was discontinued on the thirteenth day following the occurrence of the spontaneous pneumothorax. It was of interest to estimate the amount of air that could be removed when the two Stedman pumps were in tandem. One Stedman pump will aspirate air at the rate of four to five liters per minute, and presumably two pumps in tandem should aspirate at least eight liters per minute. Following discontinuation of the negative suction, there was no further dyspnea, and physical examination revealed the lung to be in the re-expanded position. The chest tubes were removed following the discontinuation of the negative suction, and the stab wounds healed promptly.

Three weeks following the spontaneous pneumothorax, a chest roentgenogram revealed the lung to be completely re-expanded, except for a small apical cap.

Examination five months following the pneumonectomy and three months following the occurrence of the spontaneous pneumothorax revealed the patient to be in good physical condition. He had gained nine pounds in weight, his sputum was negative for *M. tuberculosis*, and he was apparently none the worse for his pneumonectomy, cardiac complications, and spontaneous pneumothorax.

COMMENT AND SUMMARY

The occurrence of spontaneous pneumothorax following pneumonectomy is rare. The occurrence of a contralateral spontaneous pneumothorax following lobectomy has been reported by Gleason and Kent (1). In the case herein reported the spontaneous pneumothorax occurred two months following a left pneumonectomy. In the immediate postoperative course, the patient also suffered with auricular flutter and auricular fibrillation, but eventual complete recovery occurred.

REFERENCES

(1) Gleason, G. E., and Kent, E. M.: Contralateral spontaneous pneumothorax following lobectomy, J. Thoracic Surg., 1949, *18*, 473.

Letters to the Editors

To the Editors of the American Review of Tuberculosis:

I am very grateful for the extensive review of my book, *The Achievements of BCG Vaccination*, in the November issue of THE AMERICAN REVIEW OF TUBERCULOSIS. I hope you will allow me to verify just one very important point in the review. The reviewer has given the readers the impression that, in studying the efficacy of BCG vaccination, I have statistically compared the whole BCG-vaccinated group with a control group consisting of nonvaccinated, recently naturally infected persons. The reviewer characterizes this procedure as follows: "Such experimental methods immediately destroy any value to be obtained from a study of tuberculous mortality statistics." I agree with him in his criticism of such methods for statistical comparison. *But the fact is that I have never used such a comparison.* The reviewer has forgotten to quote the sentence on page 30 in my book just preceding the sentence he did quote in his review. The omitted sentence reads: "It" (the control material) "must be comparable with the superinfected part of the B. C. G. material." The superinfected part consists of 1,900 persons of a total of 13,500 persons in the BCG group.

A capital point in my studies of BCG problems is a method for distinguishing between vaccination allergy and superinfection allergy. The definitions of these two terms are as follows: Vaccination allergy is positive tuberculin sensitivity *due only to BCG*. Superinfection allergy is vaccination allergy completed with an "allergy resulting from a superimposed natural infection with tubercle bacilli" (Aronson). The scientific reliability of my method for distinction between vaccination allergy and superinfection allergy may be a matter for discussion. The basic arguments for the method used are broadly discussed in chapters 11 and 20 in my book. (A paper on this subject will soon be printed in *Acta tuberculosea Scandinavica*.)

Provided my method of the above-mentioned distinction is endorsed, the statistical analysis performed should give an approximately correct picture of the immunity afforded by BCG vaccination. Only the superinfected part of the BCG-vaccinated group has been put to the test, at the risk of developing tuberculosis. An adequate control group *to the superinfected part of the BCG group* should be a group of nonvaccinated persons recently naturally infected with tuberculosis. The statistical units used for comparison are, on the one hand, BCG-vaccinated persons superinfected during one year; and, on the other hand, the control group consisting of nonvaccinated persons naturally infected with tuberculosis during one year.

OSLO, NORWAY
January 24, 1950

GERHARD HERTZBERG

To the Editors of the American Review of Tuberculosis:

I have read Dr. Hertzberg's letter concerning my review of his book, *The Achievements of BCG Vaccination*, and I think it would be advantageous to quote the two paragraphs of the book from which my excerpt was taken.

"To serve as controls, persons must represent, as far as possible, an adequate or statistically uniform basis for comparison with the BCG material. The control material must present as correct a picture as possible of the risk run by exposure to natural tuberculosis infection. It must be comparable with the superinfected part of the BCG material.

"The main qualification for inclusion in the control material is the evidence (in our records) of recent infection with tuberculosis in persons who had earlier been tuberculin-negative. It is also necessary that a radiological examination shall have been made of the person in question when a positive reaction to tuberculin was demonstrated for the first time" (pages 30–31).

This would seem to indicate that all controls gave "evidence of recent infection with tuberculosis," whereas all cases vaccinated with BCG had negative tuberculin reactions before vaccination.

NEW YORK CITY
March 3, 1950

MILTON I. LEVINE

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

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CLINICAL STUDIES, TUBERCULOSIS

Lower Lobe Tuberculous Cavities.—Among 658 tuberculous patients, 43 persons with lower lobe cavities were observed. All had bacteriologically positive sputum. All were treated with one or more of the following collapse measures: pneumothorax pneumoperitoneum, phrenic crush, extrapleural pneumothorax, and thoracoplasty. In 10 cases, the lesion was in a lower lobe only. In the rest, there had been a spread from an upper lobe lesion. The lesions were more often in the dorsal than in the basal segment and more often on the right than on the left. In 5 cases, the cavity appeared to be of the "tension" type. In more than half, it was closed by collapse measures; pneumoperitoneum, preceded by phrenic crush, was responsible for three-fourths of the good results, the dorsal cavities responding better than the basal ones. Most good results were achieved in the first six months of treatment and success was proportionate to the degree of rise of the diaphragm. There were no untoward effects from very high rises. Pneumoperitoneum failed in one-third of the cases. The causes were: large size of the cavity, thick wall, very active surrounding disease, extensive costophrenic adhesions, tension cavity, cavity filled with fluid, and emphysema and fibrosis. There were few complications such as effusion and scrotal hernia. Pneumothorax was ineffectual for dorsal cavities and fairly good for basal. Spread of the disease occurred in less than one-fourth of the patients during therapy.—*Cavities of the lower lobe in pulmonary tuberculosis: Pathology and treatment with special reference to pneumoperitoneum, B. Rozenblatt, Brit. J. Tuberc., July, 1949, 43: 47.*—(*A. G. Cohen*)

Prognosis of Closed Cavities.—Roentgenographic and clinical studies of 147 patients with 183 closed cavities were made to determine their long-term prognosis. The follow-up period ranged from several months to 22 years: It was one to five years in 50 per cent of cases, more than five years in 25 per cent of cases, and less than one year in the remaining 25 per cent. The size of the density after cavity closure was chosen as a criterion for evaluation. According to their mean diameter the healed cavities were considered "large" (more than 1 cm.), "medium-sized" (3 to 10 mm.), and "small" (2 to 3 mm.), or "very small" (less than 2 mm.). This arbitrary classification gave the best correlation with the prognosis of the cases. Large healed cavities were found only in 14.8 per cent of the cases; in 3 of 4, the cavity reopened. Only one of 15 of the medium-sized healed foci opened later. Reopening of cavities in densities smaller than 3 mm. was rare. The poor prognosis of the larger foci was attributed mainly to their greater content of caseous material. The volume of the closed cavity reflected only its own prognosis and had no correlation to progression of the disease in other parts of the lungs. With the exception of thoracoplasty cases, the prognosis of healed cavities did not vary with the therapeutic procedures used. The percentage of cavities remaining closed was equal whether healing had occurred spontaneously or during pneumothorax.—*Le pronostic des cicatrices cavitaires d'après leur aspect radiologique, A. Bernou & J. Tricoire, Rev. de la tuberc., 1949, 13: 778.*—(*V. Leites*)

Reopening of Inspissated Cavities.—Of 313 tuberculous cavities which were carefully followed in an earlier study, 54 appeared to be inspissated; in 33 per cent, relapse occurred *in situ*. Another series of 129 inspissated cavities was observed from 1947 to 1949. Of these, 63 had developed without collapse therapy: the cavity repoened in 17 instances (26 per cent). The observation period in 13 cases was less than one year; in 31 cases, one to five years; in 8 cases, five to ten years; in 10 cases, ten to twenty years; and in one case, twenty-seven years. Three of the 17 cavities which reopened closed spontaneously a second time. Inspissation of 53 cavities occurred during pneumothorax. In 35 of these, collapse had been discontinued after the usual length of time; in 17 of the cases, there was relapse *in situ*. One relapse occurred after fourteen years had elapsed since re-expansion, 4 relapses after two to three years had elapsed, 2 after three years, one after four years, 2 after five years, one after six years, and 3 after eight years. These figures are of only relative value since most patients who have inspissated cavities and are well clinically do not remain under medical supervision so long after re-expansion of the pneumothorax. Of 6 inspissated cavities treated with phrenic nerve paralysis, 3 reopened after one to five years. Two of these closed again while the patients were on bed rest; one, after the phrenic nerve was crushed a second time. Three of the 6 large inspissated cavities collapsed by thoracoplasty reopened. The over-all incidence of reopening of inspissated cavities in the current series was 33 per cent. Since the follow-up period for some of these patients is still short and others still have pneumothoraces, more of their inspissated cavities may be expected.—*Nouvelles recherches sur les cavernes pleines, A. Bernou & J. Tricoire, Rev. de la tuberc., 1949, 13: 959.—(V Leites)*

Tuberculosis After Fifty.—The conception that pulmonary tuberculosis is a rarity in old age has no basis of fact. Of the 70 patients in the small sanatorium for men at Jacarepagua, Brazil, during 1949, 36 (51 per cent) were over 50 years of age, and the 2 oldest were in the 71 to 75 age group. The sanatorium stay was from six months to sixteen years, averaging two to three years. In 24 (67 per cent) of the 36, the disease had begun ten months to two years before and in the other 12 from two to sixteen years earlier. Clinically, 32 cases were fibrocavitary; 3, cirrhotic; and one, ulcerocaseous. Three patients had minimal lesions; 27, moderately advanced lesions; and 6, far advanced lesions. In 28, the sputum was bacteriologically positive. As a rule the patients benefited from the sanatorium regimen.—*A tuberculose pulmonar depois dos 50 anos, J. Moyses, Rev. brasil. de tuberc., July–August, 1949, 17: 323.—(A. A. Moll)*

Uterine Tuberculosis.—Cultures of the menstrual discharge of 16 women, in whom endometrial biopsy had established the diagnosis of endometrial tuberculosis, showed tubercle bacilli in 6 patients. Cultures of the menstrual discharge of 84 women with primary sterility, in whom endometrial biopsy had shown no sign of genital tuberculosis, were positive for tubercle bacilli in 5 patients. —*Mycobacterium tuberculosis in uterine discharge, detection by cultures: Diagnostic and prognostic value in latent female genital tuberculosis, I. Halbrecht, J. A. M. A., February 4, 1950, 142: 331.—(H. Abeles)*

Erythema Nodosum in Tuberculosis.—An "invertor" to tuberculin is considered a person who gives a positive reaction within one year after a negative test. Of 2,310 "invertors" observed, 125 (5.4 per cent) had erythema nodosum. This group was analyzed according to age and sex. Significant numbers in each age group were affected up to the age of 30 in males and 40 in females. In each age group there was a greater incidence in females. Most of the cases were in children or women. There was a greater likelihood of an "invertor" having abnormalities in the roentgenogram if he also had erythema nodosum. The low incidence of the lesion in Britain and the United States as compared to that in the Scandinavian countries is the subject of speculation.

Perhaps, because of earlier industrialization in the former countries, the population has developed a greater immunity.—*The frequency of erythema nodosum among invertors, Tubercle, February, 1950, 31: 33.—(A. G. Cohen)*

Tuberculin Reactions after Antihistaminics.—Twenty cases of tuberculous children with positive tuberculin patch tests were re-tested during and after the use of two antihistaminic drugs. No inhibition of the tests occurred. This confirms other recent work in adults.—*The effect of antihistaminic drugs on the tuberculin patch test, E. L. Kendig, Jr., W. P. Spencer, & C. W. LaTratta, J. Pediat., December, 1949, 35: 750.—(W. H. Oatway, Jr.)*

Technique of Pneumothorax Induction.—Some authors have contended that, in pneumothorax induction, most of the air found in the pleural cavity enters it by leakage from the lung which inevitably is punctured. The authors subscribe to this opinion. Accordingly they have practiced the technique of inducing pneumothorax by puncturing the lung without introducing air. A one and one-half inch, 24- to 26-gauge needle is attached to a 2 cc. syringe filled with procaine. This is inserted intercostally. When the sensation of passing the parietal pleura is detected, the needle is inserted slowly, simultaneously with traction on the piston of the syringe. The appearance of air bubbles indicates that the lung has been punctured. The needle is then withdrawn and the patient is permitted to walk around. A roentgen film is taken twelve hours later. The method was used in 106 cases. It was successful in 86. In 9 others, the classical method succeeded where the puncture method had failed. The amount of collapse was classified as marginal in 26 per cent, slight in 35, and moderate in 49. There were no cases of air embolism or tension pneumothorax.—*The pulmonary puncture technique for the induction of artificial pneumothorax, S. A. Levy, S. H. Dressler, & A. Hurst, Tubercle, February, 1950, 31: 35.—(A. G. Cohen)*

Bilateral Pneumothorax.—"Mediastinal air block" occurred in a parturient woman whose chest was roentgenographed frequently during the development of the syndrome. The respiratory effort during labor and the straining with closed glottis produced alveolar distention. This was aggravated by an endobronchial obstruction, probably a mucus plug, which resulted in atelectasis. As a consequence of the compensatory alveolar dilatation, alveoli ruptured and air escaped into the perivascular sheaths. Subsequently air erupted into the mediastinum and the deep cervical tissues, finally entering the right pleural cavity and producing severe pain in the right side of the chest. With continued leakage of air into the right pleural cavity, tension increased and ultimately air entered the left pleural cavity through a second rent in the mediastinal septum. This second pneumothorax was heralded by the spread of pain to the left side of the chest. Thus the malignant symptom complex of "mediastinal air block" was produced.—*A case of bilateral pneumothorax, associated with pneumomediastinum, atelectasis, pulmonary edema, and subcutaneous emphysema, occurring during labor: mediastinal air block, N. J. Furst & L. R. Lawrence, Am. J. Roentgenol., December, 1949, 62: 798.—(T. H. Noehren)*

Extrapleural Pneumothorax after Lobectomy.—Resection of the right upper and right middle pulmonary lobes was performed for a tuberculous giant cavity in the right upper lobe of a 17-year-old patient. A new lesion in the right lower lobe was brought under control by extrapleural pneumothorax. This procedure sometimes may be preferable to post-excisional thoracoplasty when it is important to conserve pulmonary function and when the possibility of subsequent contralateral collapse has to be considered. Extrapleural pneumothorax can only be carried out when the postoperative course after excisional surgery is entirely without complications and the pleural involvement has been minimal.—*Réalisation d'un pneumothorax extra-pleural chirurgical après exerèse lobaire supérieure pour tuberculose, M. Berard, R. Aribehaute, & A. Car-*

raud, Rev. de la tubere., 1949, 13: 969.—(V. Leites)

Pneumoplasty for Tuberculosis.—The postoperative management has been studied in 20 cases of pneumoplasty. Air refills to replace the extrapleural fluid are begun on the fourteenth day. They are continued until recalcification appears by the sixth to eighth week. The patient is then allowed out of bed. A lengthy physiotherapeutic regimen, as for thoracoplasty, is not required. Deformity is absent.—*The post-operative course of pneumoplasty and its management, J. H. Gifford, Thorax, December 1949, 4: 238.—(A. G. Cohen)*

Pneumoplasty for Tuberculosis.—A new operation for tuberculosis in lieu of thoracoplasty is proposed. The fourth and fifth ribs are resected and an extensive extrapleural pneumonolysis performed. The second to seventh intercostal bundles with the rib periostea are mobilized, detached posteriorly, and reattached to the side of the vertebral column at a lower level. During the immediate postoperative period, the lung is held down by liquid in the extrapleural space, supplemented, if necessary, by temporary air refills. Eventually recalcification occurs and prevents re-expansion of the lung. The advantages are the elimination of deformity and the performance of the operation in one stage. The operation has been performed for 37 cases. Sputum which previously was bacteriologically positive became negative in 75 per cent. Some of the failures were in early cases before the technique was fully developed. The causes of failure were re-expansion of the anterior part of the apex, uncollapesd tension cavity, too extensive disease, and contralateral disease. There were no operative deaths. Infection occurred in one case. The operation is not likely to be successful if the disease extends beyond the upper third of the lung, or if the anterolateral segment is heavily involved. It is also useful in cases where lobectomy is undertaken but cannot be completed because of a densely adherent pleura.—*Pneumoplasty: Periosteo-plastic pneumonolysis, F. R. Edwards, Thorax, December, 1949, 4: 224.—(A. G. Cohen)*

Air Embolism During Thoracoscopy.—During a thoracoscopy, several adhesions had been cut when the patient suddenly developed convulsions and died. It was assumed that death was the result of cerebral air embolism. This was confirmed by the finding at necropsy of bubbles of air not only in the basilar artery and circle of Willis but also in the superior sagittal sinus and cortical veins. The arterial emboli were thought to have originated in the lungs and then to have been carried through the pulmonary veins and the left heart into the arterial circulation. The venous emboli may have entered the cerebral circulation through the paravertebral plexus, which has communications with veins in the chest.—*Death from cerebral air embolism during thoracoscopy, P. P. Philip, Thorax, December, 1949, 4: 237.—(A. G. Cohen)*

Decortication of Tuberculous Lung.—Decortication of a nonexpanding tuberculous lung following pneumothorax was successful in 7 cases. Decortication is desirable to prevent tuberculous empyema or the impairment of respiration and circulation incident to mediastinal shifting. A possible objection to decortication is danger of reactivation of underlying tuberculous disease by the trauma of operation and too early expansion. There was no activation or spread in the series reported when streptomycin, 1.0 gm., was given daily for at least five days before and ten days after operation. If pulmonary compression is desired, it should be done selectively according to plan. The greatly thickened pleural membrane renders futile attempts at selective compression by thoracoplasty. It is logical to remove the tuberculous membrane, permit the lung to expand if it will do so, and later perform the indicated compression therapy in a purposeful manner. Thoracoplasty was performed after decortication in 2 of the reported cases. It was possible to remove all or almost all of the diseased membrane in each case. The thorax was entered

through an interspace, usually the fifth, without resecting or dividing a rib. Removal of the parietal membrane is recommended not only to permit increased function of the the chest wall and to remove a possible focus for infection, but to facilitate the operative dissection. Primary healing followed in all cases. Lacerations in the lung were closed by interrupted sutures of No. 60 cotton, including pieces of Fibrin Foam over the larger rents.—*Decortication of the unexpanded tuberculous lung following pneumothorax, J. Weinberg & J. Davis, J. Thoracic Surg., June, 1949, 18: 803.*—(*R. E. MacQuigg*)

Fiberglas for Collapse Therapy.—In one series of dogs extrapleural packing with Fiberglas wool resulted in unsatisfactory tissue reactions. In a second series Fiberglas fabric was used to wrap one pulmonary lobe, and gave selective atelectasis with minimal tissue reaction. In 3 patients an upper lobe was wrapped in Fiberglas fabric for selective collapse, and in 7 others an extrapleural pneumonolysis was done. In 6 of the latter the space was lined with Fiberglas fabric and then filled with wool; no infection resulted and the collapse was regarded as satisfactory. —*Experimental and clinical study of collapse therapy using Fiberglas wool and fabric, T. O'Neill, H. Ramirez, and R. Trout, J. Thoracic Surg., April, 1949, 18: 181.*—(*R. E. MacQuigg*)

Lucite Plombage.—Fifty-one cases of plombage with lucite balls were followed from one and a half years to two years and ten months. In this series 10 patients were improved, 3 did not improve, 20 were worse, and 18 died. Once the spheres were inserted they were extremely difficult to remove unless the surrounding tissue was liquefied by infection. The late results of the operation as performed at Duke Hospital did not justify continuation of the procedure.—*An evaluation of extrapleural pneumonolysis with lucite plombage, J. Trent, J. Moody, & J. Hiatt, J. Thoracic Surg., April, 1949, 18: 173.*—(*R. E. MacQuigg*)

Angiocardiography in Tuberculosis.—The pulmonary circulation was studied with angiocardiography in 23 tuberculous patients, 8 of whom had therapeutic pneumothorax. The diminution of circulation, although present in most cases of pneumothorax, was of an extremely variable degree. In some patients the blood supply was practically absent; in others, hardly decreased. In some patients with pneumothorax the diseased area was selectively excluded from the circulation, the remainder of the collapsed lung being almost normally vascularized. This finding of a diminished blood supply in the collapsed lung brings up the question of timing streptomycin therapy in relation to pneumothorax. It seems logical to administer the antibiotic prior to the institution of collapse and illogical to employ streptomycin and pneumothorax simultaneously. Of 15 patients with caseous-cavernous disease studied by angiocardiography, 3 were not given streptomycin because no circulation was seen in the diseased area. In 11 patients there was correlation between the degree of vascularization and the result of streptomycin treatment. Thus 5 patients had lesions which were undoubtedly excluded from the circulation and their streptomycin therapy was a complete failure. In 6 others, the blood supply around the cavity seemed normal and streptomycin gave substantial results, with prompt closure or considerable diminution in the size of the cavity. Since 10 to 15 per cent of all cavities close during streptomycin therapy, it might be advisable to determine the blood supply of a cavity if pneumothorax cannot be induced. Thus the chances for success with streptomycin therapy might be determined before resorting to surgical procedures. The same applies to bilateral cavitary lesions.—*L'intéret de l'angio-pneumographie chez les tuberculeux pulmonaires, Pierre-Bourgeois, M. Durand, Vic-Dupont, P. Y. Hatt, & M. K. Caramanian, Semaine d. hôp., February 6, 1950: 427.*—(*V. Leites*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Sarcoidosis in Siblings.—In a family of 5 brothers and 2 sisters, 2 of the brothers were found to suffer from sarcoidosis. The literature contains records of several similar situations.—*The familial aspects of sarcoidosis, E. R. Bickerstaff, Brit. J. Tuberc., October, 1949, 43: 112.*—(*A. G. Cohen*)

Emphysematous Cavity.—A case of emphysematous pulmonary cavity is reported because the patient was observed during an unusually long follow-up period. She was found to have a normal chest when fluoroscoped at the age of five years. At the age of six she had a respiratory infection, developed a hilar infiltration which was noted four months later, and showed signs of a cavity two months after that. Her tuberculin test was negative. Twenty-one years later she was seen to have the same lesion, unchanged in size, asymptomatic in spite of a fluid level. The tuberculin test was then positive. The previous history helped prove that it was a noncongenital, nontuberculous, chronic emphysematous cavity.—*Chronic emphysematous cavity of the lung, H. Vollmer, Am. J. Dis. Child., November, 1949, 78: 755.*—(*W. H. Oatway, Jr.*)

Congenital Cystic Lungs.—Although congenital cystic disease of the lung often produces symptoms from childhood, 35 patients of various ages referred to the University of Chicago clinics were shown to have the condition; in only one had the diagnosis been previously suspected and made. The pathology has been known for years, and fundamentally it consists of a maldevelopment of the bronchial elements. There are 3 general clinicopathologic patterns: (*1*) solitary or multiple large cysts surrounded by normal lung tissue, (*2*) multiple grape-sized lesions, and (*3*) multiple small cystic spaces in the midst of fetal nonaerated lung tissue. The disease should be suspected when chronic suppurative lesions do not respond to therapy, when areas of nontuberculous pneumonitis and infiltration do not respond, and when roentgenograms are suggestive. Apparently the medical profession is not generally familiar with the condition.—*Congenital cystic disease of the lung, D. E. Cassels, J. M. Fritz, & W. E. Adams, J. Pediat., November, 1949, 35: 585.*—(W. H. Oatway, Jr.)

Pleural Effusion in Newborn.—Only 10 cases of pleural effusion in infants less than one year old have been reported in the American literature since 1910; all were chylous. A case is reported in which a nonchylous effusion was found fifteen hours after birth. Thoracentesis on five occasions yielded a clear, dark orange fluid. The first specimen contained bile but later ones did not. No microorganisms could be demonstrated in the fluid. It ceased to form after twenty-seven days and the pleural changes had disappeared on the forty-fifth day. The course throughout was afebrile. Two possible causes, traumatic pleurisy and concealed pneumothorax, seem improbable.—*Spontaneous pleural effusion in a newborn infant, D. W. Cugell & S. Scherl, Am. J. Dis. Child., October, 1949, 78: 569.*—(*W. H. Oatway, Jr.*)

Pathogenesis of Bronchiectasis.—Roentgenology has changed the concept of the pathogenesis of bronchiectasis. Obstructive atelectasis and related conditions with localized impaired ventilation are important mechanical forces dilating the bronchi. Every bronchogram illustrates this fact by revealing non-filling of the branches distal to the dilated bronchi, the so-called "leafless tree." Patches of pneumonic consolidation or emphysema, if suitably distributed, destroy the normal cushioning of resilient parenchyma and so exert a dilating pull upon the bronchi. Atelectasis and fibrosis with shrinkage produce rigidity and an outward, contractile strain, thus augmenting the pathologic traction upon the bronchial walls. In early cases, return of dilated bronchi to normal width has been observed with subsidence of the parenchymatous changes which caused the mechanical disturb-

ance. Those observations, supported by the pathologist's finding that the destruction of bronchial structures is not adequate in most cases to account for the bronchial dilatation, have disproved the theory that destructive changes are a prerequisite or first step in the dilatation of bronchi.—*The pathogenesis of bronchiectasis, a roentgen contribution, F. G. Fleischner, Radiology, December, 1949, 53: 818.*—(*W. J. Steininger*)

Poliomyelitic Respiratory Disorders.—Paralysis and spasm are the muscular changes in poliomyelitis; the latter is reported to be a local disorder of the muscle. During the 1946 Minnesota epidemic, muscular weakness was noted in 65.4 per cent of 1,125 patients, and spasm of some area was present in all. A group of 368 patients was carefully studied; 43 had respiratory disorders. Death occurred in 18 of these 43 cases and in 16 of the 18 was due to the breathing disorder. Four general causes of respiratory difficulty were noted: spasm of chest muscles, paralysis of chest muscles, paralysis of the respiratory center, and polio-encephalitis. Spasm, which causes muscles to contract and shorten, produced pain, tenderness, dyspnea, tachypnea, and limited excursion of the chest. It affected intrinsic, extrinsic, or diaphragm musculature and was treated by hot packs. The use of a respirator was avoided, if possible, since it interfered with the application of packs and aggravated spasm. Spasm of the chest muscle was a serious cause of breathing difficulty in 38 of the 43 cases. Muscular weakness or paralysis was present in 12 of the 43 cases and was the cause of death in 4 patients. The signs were those of a progressive loss of excursion, with dyspnea, cyanosis, and rapid, shallow respirations. Paralysis often was accompanied by spasm and, if the former was predominant, packs had to be replaced by a respirator. Bulbar lesions were fatal in all 7 of the cases in which they occurred. Respirations were not irregular as has been reported and breathing was easily synchronized with the respirator. Facial and oral signs preceded and warned of the failure of the respiratory center. Polio-encephalitis occurred in 26 of the 368 cases, and was lethal in 7 of them. After the early stages of irritability and apathy, respirations became Cheynes-Stokes in character and the patients could not cooperate with the respirator, which seemed to be contraindicated.—*Disorders of the respiration in bulbar and other forms of poliomyelitis, with special reference to muscle spasm, J. F. Pohl, Arch. Pediat., December, 1949, 66: 537.*—(*W. H. Oatway, Jr.*)

Pyocyaneus Tracheobronchitis.—A male infant aged ten weeks developed tracheobronchitis and survived for eight weeks. Administration of sulfonamides, penicillin, streptomycin, and polymixin were unavailing. Necropsy showed a purulent bronchitis and pneumonia. *Pseudomonas pyocyaneus* was cultured from the secretions. One year later a newborn sister developed a similar condition and survived for nine months. The same organism was recovered.—*Fatal chronic tracheobronchitis due to pseudomonas pyocyaneus in two siblings, J. R. O'Brien, Lancet, January 14, 1950, 1: 169.*—(*A. G. Cohen*)

Pneumoconiosis from Coke Fires.—Workers were exposed to irritant "sulphur" fumes and dust arising from open coke fires while working near them or during intervals of hand-stoking. The trades involved were boiler-stoker, blacksmith, and plater and also employees in coke-oven and gas works. The risk was not great in larger gas works where adequate ventilation is provided. Ten workers with positive roentgenographic findings were seen. All had symptoms; chiefly cough, exertional dyspnea, and irritation of the nose, throat, and conjunctiva. There was no relation between the intensity or length of exposure and the severity of symptoms. Physical signs were not specific. The sputa were negative for tubercle bacilli. Roentgenograms showed irregular patchy fibrosis in both lungs, usually predominant on one side. In most cases the mid and lower zones showed nodulation which had occasionally produced, by confluence, patchy consolidation. Emphysema was always

present. It is believed that this is a hitherto undescribed form of pneumoconiosis. The dust was analyzed and was found to include fine particles which contained free silica and some iron. Nevertheless, ships' firemen do not develop these changes which also are not similar to those seen in ironworkers. Moreover, sulphur dioxide alone is not known to cause changes. It is believed that the sulphur dioxide causes localized chronic inflammatory changes in which the dust later accumulates.—*Pneumoconiosis after exposure to sulphur dioxide fumes and dust from coke fires, L. Duner, R. Hardy, & D. J. T. Bagnall, Lancet, December 31, 1949, 2: 1214.*—(*A. G. Cohen*)

Kerosene Pneumonia.—Through carelessness in the storage of kerosene, the accidental ingestion of this product is not uncommon in certain parts of this country. In children, the kerosene is likely to be aspirated, leading to a chemical pneumonitis which in turn is a favorable environment for infection. Chest roentgenograms were made on 60 children who developed pneumonia following the ingestion of kerosene. In all cases the roentgenographic changes were confined to the lower lobes; they were practically always bilateral. In mild cases, the changes consisted of only a mild diffuse haziness of the cardiophrenic angles. In moderately severe cases, there were confluent patchy areas of consolidation throughout both lower lobes, while in the most severe cases the confluence and consolidation were so extensive as to be considered lobar. The roentgenographic manifestations of kerosene pneumonitis are not pathognomonic. They are most pronounced 24 to 36 hours after ingestion of the offending substance and usually completely clear by the third day.—*Pneumonia in children following the ingestion of petroleum products, C. H. Heacock, Radiology, December, 1949, 53: 793.*—(*W. J. Steininger*)

Tetraethylammonium Chloride for Chest Pain.—By a chance observation, intravenous tetraethylammonium chloride was found to relieve the pain caused by pulmonary infarction. The drug then was tried in a series of 40 cases in which there was chest pain from infarction, trauma, pneumonia, pleuritis, tuberculosis, and neoplasm. The drug was given intravenously slowly in a concentration of 100 mg. per cc., the blood pressure being checked during administration. The injection was stopped if the blood pressure fell; this was found only in older patients. Originally 3 or 4 cc. were given; this was tolerated in younger patients. Now, the dosage used is 3 mg. per kg. The patient is kept in a recumbent position for thirty minutes after the injection. In all cases, the pain was diminished; in most cases, this benefit was marked and prolonged. Better relief was obtained in younger individuals. The mode of action is not known; the drug is not a general analgesic. It is to be used with caution in the presence of hypertension and arteriosclerosis. —*Relief of chest pain by tetraethylammonium chloride, H. L. Israel, E. L. Keefer, F. E. Urbach, & W. D. Willis, New England J. Med., November 10, 1949, 241: 738.*—(*A. G. Cohen*)

Postoperative Pulmonary Stasis.—The tendency for atelectasis and pneumonia to develop after surgical procedures may be initiated by hidden factors. An important but ignored factor is the stasis of blood in the lungs. Other factors such as retained secretions, aspiration of foreign material, pulmonary embolism, and primary bacterial invasion have been stressed. The increase in fluid content of the lung is of great importance since it results in a decreased air content. It occurs because the lung is a major blood reservoir which becomes overloaded when the muscular inactivity and depressed functional state of the patient allows a pooling in the pulmonary low-pressure area. Position may play a significant role in the distribution of the accumulated blood and special procedures may be necessary to prevent pulmonary complications.—*Blood stasis in the lungs as a factor in the etiology of postoperative pulmonary complications, H. C. Maier, Ann. Surg., October, 1949, 130: 790.*—(*W.H. Oatway, Jr.*)

Pulmonary A-V Aneurysm.—Arteriovenous aneurysms in the lungs as a rule are congenital and often occur with other vascular disorders of hereditary nature such as telangiectasia. Pathologically the lesion is a sack lined with endothelial cells and surrounded by a wall which may be thick and firm, containing calcified portions, or so thin as to perforate with hemoptysis or intrapleural bleeding. An enlarged artery, sometimes dilated in a necklace fashion, as well as one or more enlarged veins supply the aneurysm. The symptoms depend upon how much blood is shunted from the artery to the left heart without the usual oxygenation in the lungs. Small pulmonary aneurysms may cause no symptoms or occasionally fatigue, dizziness, headache, cough, or chest pain. Larger aneurysms may cause cyanosis, dyspnea, polycythemia, and clubbing of the fingers and toes. Cardiac hypertrophy is seldom present. A continuous or systolic murmur usually is present over the site of the aneurysm. In the differential diagnosis it is important to note that roentgenologically the tumor-like process is connected to the hilus through broad, dilated vessels and that the shadow varies in size with changing venous pressure. Thus it diminishes when Valsalva's procedure is performed and enlarges when Müller's procedure is carried out. The diagnosis of a small aneurysm may be more difficult, for it may resemble a metastasis, a cyst, or a tuberculous focus and the variation in size may be difficult to observe. A most important feature is its relation to the surrounding vessels which are broader than the others, situated in the same region, and often conspicuous in being more sinuous and in having an unusual course. Planigraphy or angiography may ensure a more certain diagnosis. Small aneurysms probably require no more than repeated observation. Growing aneurysms, especially those associated with general changes such as cyanosis, dyspnea, and clubbing, require local dissection, lobectomy, or pneumothorax.—*Arterio-venous aneurysm in the lungs, E. Hedvall, Acta tuberc. Scandinav., 1949, Supplement 21: 32.*—(*K. T Bird*)

Pulmonary Hemangioma with Arterial Defect.—A 20-year-old white man had clubbing of the fingers and toes, cyanosis of lips, fingers, and toes, dyspnea on exertion, pain in the left chest, and two episodes of hemoptysis during the two months preceding admission. There was dullness on percussion over an area just to the left of the aortic arch and a loud crescendo systolic murmur heard best over the pulmonic area. Chest roentgenograms showed an oval area of increased density in the left upper lobe. Bronchoscopy revealed narrowing of the left main bronchus. Pulmonary arteriography by venous catheterization showed dilatation of the pulmonary artery; thoracic aortography by arterial catheterization gave no information. The patient died after a large pulmonary hemorrhage. At autopsy there was a large oval communication between the aorta and pulmonary artery and a cavernous hemangioma in the left lung.—*Pulmonary hemangioma with pulmonary artery-aortic septal defect. Attempted roentgen visualization by catheterization of brachial artery and basilic veins, L. A. Erf, J. Foldes, F. V. Piccione, & F. B. Wagner, Am. Heart J., November, 1949, 38: 768.*—(*G. C. Leiner*)

Bronchial Adenoma.—A group of 45 men and 41 women with microscopically proved adenoma of the bronchus was investigated. The average duration of symptoms before the diagnosis was established was thirty months. The symptoms were, in order of decreasing frequency: cough, hemoptysis, pain, chills and fever, dyspnea, and wheeze. Roentgenographic pulmonary changes of appreciable significance were found in 74 per cent of the 86 patients. The adenoma was demonstrated by bronchoscopic examination in 91 per cent of the patients. In 90 per cent the lesions were of the carcinoid type and in 10 per cent, of the cylindroma type. Five patients had definitely proved metastasis, in 3 others metastatic lesions were probably present. Generally infiltration in and around the bronchial wall is present in approximately 90 per cent of bronchial adenomas; the mucosa is intact over the tumor, which explains the

negative results of cytologic studies of the sputum. The type of treatment depends on the situation of the lesion, the attachment to the bronchial wall, the age of the patient, and the degree of secondary suppuration. An adenoma which is pedunculated and situated in a bronchus from which its removal can readily be accomplished is best treated bronchoscopically. Patients of advanced years and those whose lesions are situated close to the carina, so that a pneumonectomy would have to be performed, are also best treated by bronchoscopic means. Repeated bronchoscopic examinations are necessary after the treatment because of the possibility of recurrence. Surgical treatment is indicated in all other cases and in cases in which the tumor shows evidence of recurrence.—*Bronchial adenoma, H. J. Moersch & J. R. McDonald, J. A. M. A., February 4, 1950, 142: 299.—(H. Abeles)*

Malignancy of Bronchial Adenoma.—In 5 patients with malignant bronchial adenomas there was complete transformation to bronchiogenic carcinoma. Metastases to mediastinal lymph nodes may occur when tumors have been present for thirty years or only a few months. The failure of bronchial adenoma to produce vascular seedings, even though the tumor cells were floating in a large pulmonary vein, suggests that the only favorable soil is in bronchi and lung. Treatment by lobectomy and pneumonectomy has given approximately 100 per cent five-year cures.—*The malignant nature of bronchial adenoma, A. Goldman, J. Thoracic Surg., April, 1949, 18: 137.—(R. E. MacQuigg)*

Mediastinal Glomus Tumor.—A case of glomus tumors of a lower extremity and the mediastinum is described, the latter site being new in the literature. The patient had noted paroxysms of right lower chest pain for nine years and roentgenography revealed a mass in the posterior mediastinum. Thoracotomy exposed a 5 by 3 tumor just lateral to the eighth dorsal vertebra, apparently attached to the eighth intercostal nerve. Following the removal of this tumor and those on the lower extremity, there was no recurrence of either the tumors or the pain. Complete surgical excision of glomus tumors results in permanent cure; radiation therapy is not effective.—*Glomus tumor of the mediastinum, G. Brindley, J. Thoracic Surg., June, 1949, 18: 417.—(R. E. MacQuigg)*

Carcinoma of Upper Third of Esophagus.—Rational cancer surgery requires removal of the entire gland-bearing area and radical extirpation of the lesion. Lesions above the aortic arch are cervicothoracic problems since from this area drainage is chiefly into the deep cervical lymph nodes. A combined cervicothoracic resection, with radical resection of the regional nodes bilaterally en bloc is recommended, although this implies the use of more than one stage. This was accomplished successfully in a 62-year-old woman. After resecting the tumor the upper stump was sutured to the skin and a pedical graft was prepared from the anterior chest wall. Five days later gastrostomy was done. Eight weeks after that the graft was inserted through the superior thoracic aperture and anastomosed to the distal stump of the esophagus as a combined cervicothoracic procedure. The patient was then fed by a tube through the new esophagostomy opening and the gastrostomy was allowed to close. The cervical skin finally was rolled over the openings to the tubed graft and the upper stump, completing the reconstruction of the esophagus. Bilateral neck dissection was not done in this case because of the complicating presence of a large goiter. Retention of active peristalsis in the distal esophagus is felt to be important in keeping the reconstructed portion sucked empty.—*The use of tubed pedicle grafts in carcinoma of the upper esophagus, E. Bricker, T. Burford & B. Eiseman, J. Thoracic Surg., June, 1949, 18: 304.—(R. E. MacQuigg)*

Substitution of Bowel for Esophagus.—In 2 cases, small bowel successfully replaced esophagus resected for lye stricture. A segment of jejunum was isolated, jejunal con-

tinuity restored by end-to-end anastomosis, and the distal end of the jejunal loop anastomosed to the fundus of the stomach. In the second stage, the chest was opened, the esophagus removed, preserving the vagi, and the upper end of the jejunal loop was drawn through the diaphragm and out of the neck beside the proximal stump of esophagus. In the third and final stage these were anastomosed with as large an aperture as possible after the mediastinum had sealed. Among the advantages of the procedure are maintenance of normal capacity and function of the stomach, with the gastrostomy undisturbed throughout the entire procedure.—*Transthoracic small bowel substitution in high stricture of the esophagus, A. Harrison, J. Thoracic Surg., June, 1949, 18: 316.*—(*R. E. MacQuigg*)

Angiocardiography.—Angiocardiography is of diagnostic value in many intrathoracic conditions. Aneurysms of the thoracic aorta and certain mediastinal tumors often resemble each other both clinically and radiologically. In angiocardiography, the contrast medium fills the aneurysm unless it is occupied by a clot or has a small opening. Tumors are not filled. Precise localization of these tumors and their relationship to the great vessels is demonstrated by this method so that operative difficulties may be anticipated. In the case of thymic tumors, there is great variation in relationship to surrounding vessels and therefore to operability. Angiocardiography helps to resolve these questions. The pressure effects of mediastinal nodes as in lymphoblastomas can be determined. This can also be shown occasionally in metastatic nodes in bronchogenic carcinoma. In the latter condition changes in the pulmonary vascular pattern occasionally may be of diagnostic value.—*Angiocardiography in thoracic surgery, I. Steinberg, C. T. Dotter, & W. DeW. Andrus, Surg., Gynec. & Obst., January, 1950, 90: 45.*—(*A. G. Cohen*)

Surface Anesthesia by Nebulization.—By nebulizing anesthetic solutions and having patients inhale them, profound surface anesthesia can be obtained from the external nares and mouth to the pulmonary alveoli, provided the size of the nebulized particles is suitable. This use of nebulization in obtaining surface anesthesia was especially designed and has been used primarily for bronchography in children. A nebulizer may be used with the accompanying hand bulb or may be connected by rubber tubing to an air compressor or an oxygen tank. The anesthetic solution used was a 0.5 per cent pontocaine solution containing 0.06 cc. (mp) of epinephrine 1 : 1,000 per cc. of solution. For the average cooperative adult and for older children, 2 cc. of the anesthetic solution were nebulized and inhaled by the patient during a ten- to fifteen-minute period. At the end of nebulization the swallowing, gag, and cough reflexes were absent except on extreme stimulation. This depth of anesthesia persisted for eight to ten minutes. Indirect laryngoscopy in apprehensive patients and passive bronchography in cooperative adults and older children have been accomplished by the use of this method. For deeper and more prolonged anesthesia, 4 cc. of the pontocaine solution was nebulized and inhaled. This required 20 to 25 minutes and gave a profound surface anesthesia which lasted an additional 40 to 45 minutes. This procedure has been used in obtaining bronchograms in children as young as four years of age. By allowing the aerosol to be continuously generated by a constant flow of oxygen, sufficient local anesthesia could be produced to obtain bronchograms in infants and young children. With this method there was a waste of material, and a greater volume of solution was introduced into the nebulizer. The advantage of this method for obtaining surface anesthesia of the respiratory mucosa is its simplicity. No positioning was necessary during anesthetization. The amount of pontocaine used was much less than in the conventional methods of anesthesia. The same precaution against reactions were taken as in any procedure involving surface anesthetics.—*Surface anesthesia of the respiratory mucosa by nebuliza-*

tion, J. B. Miller & H. A. Abramson, Quart. Bull., Sea View Hosp., January, 1949, 11: 1.—(K. T. Bird)

ANTIMICROBIAL THERAPY

PAS Treatment in Sweden.—*p*-Aminosalicylic acid (PAS) was used in the treatment of 378 cases of pulmonary tuberculosis in a cooperative study by six Swedish sanatoriums. Of these, 215 cases met the established criteria: (*1*) The diagnosis was established by guinea pig inoculation or culture, or the positive results of sputum examination were confirmed by roentgenography. (*2*) Cases of varying extent, with and without complications, were included. (*3*) The period of sanatorium observation before treatment was at least six months. (*4*) During this period the lesions were stationary or progressive. (*5*) In regard to collapse therapy, the series included cases in which (a) collapse was never employed, (b) collapse therapy was terminated at least three months before treatment with PAS, (c) collapse therapy was begun at least three months before PAS, or (d) collapse therapy never was started during the treatment with PAS. (*6*) The duration of observation after PAS treatment was at least six months. Of the 215 patients, 48 per cent were men and 52 per cent women; 73.7 per cent were between the ages of 15 and 35 years; 23.4 per cent were older. Minimal tuberculosis was present in 8.8 per cent, moderately advanced in 34.6, and far advanced in 56.6 per cent. About 60 per cent had exudative lesions and 40 per cent productive; 90 per cent had progressive disease and 10 per cent, stationary. Cavities were present in about 80 per cent. All of the patients were observed carefully for at least 60 days before treatment. Intestinal tuberculosis was present in 23.9 per cent, tuberculous empyema in 19.7 per cent, and tracheobronchial tuberculosis in 14.6 per cent. PAS was the only treatment given in 40.5 per cent of the selected cases. Collapse therapy had been used and discontinued previously in 15.6 per cent, had been begun and was continued during PAS treatment in 43.9 per cent. No other form of chemotherapy was used in the series. PAS was administered from one to three months to 30.3 per cent of the patients, three to six months to 48.8 per cent, and more than six months to 20.9 per cent. The total amount of PAS used was 0.5 kg. in 10.2 per cent, 0.5 to 1 kg. in 39.5 per cent, and 1 to 2 kg. in 42 per cent of the cases. As a result of treatment, 75 per cent of the patients became afebrile, 61.9 per cent gained weight, the sedimentation rate became normal in 53.3 per cent, expectoration diminished in 48.1 per cent and disappeared in 22.4 per cent. Previously positive sputum became negative in 28.2 per cent of the patients. There was marked decrease in the size of the parenchymal lesion in 35.5 per cent; cavities were practically closed in 18.3 per cent and diminished in 27.2 per cent. Immediate marked improvement was noted in 39.5 per cent of the patients and immediate improvement in an additional 39 per cent. Three months after the completion of the treatment, 57.6 per cent of the patients were still improving. The authors conclude that good results may be expected from treatment of pulmonary tuberculosis with PAS in cases of recent acute exudative disease, in chronic cases with exacerbations, in acute spreading disease occurring during collapse therapy, in cases where it is used as a preoperative measure, and in cases complicated by intestinal tuberculosis or other tuberculous infections of mucous membranes. Fairly satisfactory results were obtained in the 168 cases which did not meet all of the established criteria.—*Résultats du traitement de la tuberculose pulmonaire par l'acide para-amino-salicylique (PAS), G. Vallentin, Le Poumon, May-June, 1949, 5: 193.—(A. T. Laird)*

PAS for Tuberculosis.—The author, who introduced the drug to clinical tuberculosis, reports the results of a cooperative study carried out in 6 Swedish sanatoriums. A total of 378 patients was treated with *p*-aminosalicylic acid, of which it was possible to adhere to previously determined criteria in 205. Thus, it was not always possible, in

cases of fresh spread, to wait two months before therapy. Also, it was often necessary to supplement the drug by surgical therapy. The average daily dose of the drug was 14 gm. Therapy in many cases lasted as long as six months. After several weeks, there generally was a drop in temperature; the sedimentation rate rose. The body weight increased and the amount of sputum decreased. The general condition improved. There was roentgenographic retrogression in many and cavity closure often occurred. Follow-up studies showed continued improvement in many.—*PAS in pulmonary tuberculosis, J. Lehmann, Tubercle, January, 1950, 31: 2.—(A. G. Cohen)*

Intrabronchial PAS.—Intrabronchial instillation of *p*-aminosalicylic acid resulted in a closure of a large cavity which had persisted for two years despite extrapleural pneumothorax in a patient whose tubercle bacilli had become resistant to streptomycin. A total dose of 9 gm. was employed.—*Action favorable du PAS en injection intrabronchiques sur une caverne pulmonaire inerte, P. Lowys & LeBarre, Rev. de la tuberc., 1949, 13: 1005.—(V. Leites)*

PAS for Intestinal Tuberculosis.—The prognosis was considered unfavorable or doubtful in 22 patients with pulmonary and intestinal tuberculosis. All were treated with *p*-aminosalicylic acid for three to eleven months after an observation period of five to twenty-seven months. In 19 patients, the general condition made a prompt and obvious change for the better. Two patients became worse, one died. In 19 patients the intestinal symptoms disappeared after two to four weeks' treatment, in 3 others they definitely improved. Obvious regression was observed in all of the 8 fresh, exudative pulmonary lesions; 3 of the patients were discharged. In 2 instances it was possible to institute pneumothorax; in 8 others operation was made possible and 5 of these 8 underwent successful thoracoplasties. No serious toxic reactions were observed. (Author's summary) —*L'acide para-amino-salicylique (PAS) dans le traitement de la tuberculose pulmonaire avec tuberculose intestinale secondaire, B. Carstensen & S. Sjölin, Le Poumon, May–June, 1949, 5: 209.—(A. T. Laird)*

PAS for Tuberculosis.—The recorded effects of *p*-aminosalicylic acid (PAS) on patients are: (*1*) peripheral vasodilatation, (*2*) antipyresis, and (*3*) subjective improvement. The sodium salt of the drug was administered in 6 divided doses totaling 30 gm. daily to 64 patients, 53 being treated with the drug alone and 11, in conjunction with other forms of therapy. The fever fell within 48 to 72 hours, especially if it was high originally. If the temperature was normal initially it often became subnormal. The sedimentation rate fell with varying rapidity. After seventeen days, the tubercle bacilli recovered from the patients changed in appearance. Often a specimen showed many organisms on smear but little or no growth on culture. There was nausea in 32 patients and nausea and diarrhea in 22. Alkalis were not helpful but belladonna gave relief. In 3 cases, sensitization phenomena appeared, taking the form of a rash in one and hyperpyrexia in 2. Each patient was desensitized successfully. Signs of resistance of the organisms to PAS appeared within 120 days. Experimental studies in guinea pigs with blood PAS levels comparable to those in humans showed that there was no protection against a lethal challenge dose of PPD. This indicates that PAS has no tuberculin-neutralizing power. The antipyresis is produced by peripheral vasodilation which results in increased heat loss and is compensated by a rise in the basal metabolic rate. A prolongation of clotting time is produced which can be counteracted by vitamin K. The gamma globulin of the blood is unaffected. It is believed that PAS has no specific antibacterial value. Its beneficial effects are the result of: (*1*) direct action on the products of the metabolism of the tubercle bacillus (not tuberculin), and (*2*) antipyresis.—*Para-aminosalicylic acid in tuberculosis, D. G. Madigan, L. L. Griffiths, M. J. G. Lynch, R. A. Bruce, S. Kaj, & G.*

Brownlee, Lancet, February 11, 1950, 1: 239.—(*A. G. Cohen*)

Clinical Tests of Chemotherapy.—More than 200 cases of pulmonary tuberculosis have been treated at the St. Göran Hospital, Stockholm, with *p*-aminosalicylic acid (PAS) and Diasone and, since January 1947, with PAS and streptomycin. The agents were used to some extent separately. The results were evaluated by observing the body temperature and the blood, including studies of the Arneth-Schilling formula and of the sedimentation rate. Variations in body temperature and the blood reactions due to toxic effects seem to occur quite independently. The Arneth-Schilling reaction apparently is somewhat more influenced by streptomycin than by PAS. After PAS is added, an improvement of the sedimentation rate is often noted. The treatment was designed to produce a concordant effect. When the sedimentation rate and the leukocyte pattern grew worse it could be inferred that the tubercle bacilli were becoming resistant to the drugs, especially to streptomycin.—*Sur l'appréciation des résultats de la chimothérapie de la tuberculose pulmonaire, A. Westergren, Le Poumon, May–June, 1949, 5: 187.*—(*A. T. Laird*)

Blood Change with Streptomycin.—Hematologic studies were made on 65 tuberculous patents receiving streptomycin, 2 gm. daily, for twenty-five days, followed by 1.5 gm. daily until a total of 150 to 200 gm. was reached. Various types of tuberculosis were treated: fibrocaseous, fibrous, and cavernous forms, infiltrates, and tuberculous effusions. In all of these forms similar changes occurred during streptomycin therapy: (*1*) anemia of the hypochromic type, which was associated with anisocytosis and anisochromia in 40 per cent of the cases; (*2*) leukocytosis, generally with a white cell count about 12,000; and (*3*) eosinophilia of 3 to 5 per cent, in most cases during the first months of treatment. These changes were found in all patients, the anemia and leukocytosis disappearing when the dosage was reduced. Eosinophilia increasing to 6 or 8 per cent and monocytosis indicated a favorable prognosis. They were found in all patients who showed clinical and roentgenologic improvement with streptomycin. A sudden rise in the number of eosinophils above 8 per cent was cause for alarm. It was observed in all instances of cutaneous complications such as urticaria, angioneurotic edema, and eczema. A sudden drop in the eosinophil count was a prognostically unfavorable sign. The danger of agranulocytosis has to be considered if there is decrease in leukocytes in the first months. Isolated mononucleosis always was associated with icterus.—*Étude de la formule sanguine au cours du traitement de la tuberculose pulmonaire par la streptomycine, L. Isemin & Mlle. Fourcade, Semaine d. hôp., Paris, November 30, 1949, 3: 679.*—(*V. Leites*)

Streptomycin for Childhood Tuberculosis.—Streptomycin was administered to 48 tuberculous children, each of whom had: (*1*) a positive Mantoux test; (*2*) gastric washings or bronchoscopic aspirations containing tubercle bacilli, confirmed by cultures and guinea pig inoculations; (*3*) roentgenograms showing pulmonary infiltrations, usually of an advanced degree; and (*4*) close medical supervision for at least three months before treatment. Of the 48 patients treated, 41 were classified as having a progressive primary lesion and 7 as having far advanced, adult-type pulmonary tuberculosis with large cavities. The progressive primary lesions were found in children aged eight months to eleven years. The adult type of lesion occurred in children from eleven to fourteen years of age. Twenty-nine children were Negroes, 6 were Mexican, and 13 were white. There were 19 boys and 29 girls. The daily dose of streptomycin was 0.5 gm. intramuscularly in the early cases and 0.3 gm. in the later cases. The duration of treatment varied from 120 to 60 days. With 0.3 gm., blood levels reached 6 to 8 γ of streptomycin per cc. six hours after intramuscular administration. Clinical response was satisfactory in all cases, improvement starting a week or ten days

after the beginning of therapy, and characterized by a drop in temperature, improvement in appetite, and lessened irritability. Roentgenographic changes appeared more slowly. Tubercle bacilli disappeared from the sputum in 42 of the 48 cases. Two patients had tuberculous sinuses associated with underlying bone infections. One was a 12-year-old boy with a residual draining sinus at the elbow for two years who had had several operations. After two weeks of streptomycin therapy the sinus closed and has remained closed during the year and a half since cessation of streptomycin therapy. The second patient was two years old and had a sinus in the supra-orbital bone; this failed to respond to conservative measures. One month after the start of streptomycin therapy, the sinus closed.—*Tuberculosis in infants and children treated with streptomycin, E. T. McEnery, M. Clin. North America, January, 1950, p. 271.*—(*L. Hyde*)

Intraventricular Streptomycin.—The intrathecal administration of streptomycin was abandoned because the procedure was often difficult and painful, and was dangerous in patients with papilledema and stasis. It might lead to exacerbation of the process in the meninges as well as being irritating and often ineffective. Intraventricular administration was found to be a simple and painless procedure, well tolerated by the patients, and free from after effects such as vomiting or headache. The patients could remain in their usual position after the injection. This method allowed diagnostic examination of the intraventricular fluid. It gave marked relief from such symptoms as headache, vomiting, and psychic disturbances. Of 20 patients with tuberculous meningitis treated intraventricularly, 12 had a poor prognosis because of age or associated pulmonary lesions; 12 reached the stage of convalescence.—*La streptomycinotherapie intraventriculaire systématique des meningites tuberculeuses, P. Nayrac, E. Laine, M. Fontan, M. Coudemand, G. Niquet, A. Clay, & P. Warot, Semaine d. hôp. Paris, October 30, 1949: 3311.*—(*V. Leites*)

Tuberculous Cystic Osteitis.—Multiple cystic tuberculous lesions of the bones are still uncommon enough to be reported and it is even more notable when the disease is successfully treated. The condition often is associated in adults with a negative tuberculin reaction and a clinical picture suggesting sarcoidosis. In children the skin tests are usually positive; caseation may be noted; animal inoculation may be positive for tubercle bacilli; and the patient often dies of generalized tuberculosis. The eighteenth proved case in a child is reported. The patient was a 19-month-old Negro infant with a family history of tuberculosis, a positive tuberculin test, and a swelling of one month's duration on the dorsum of the right hand. He was febrile, anemic, and had a leukocyte count of 20,000. Roentgenograms showed a defect of the right third metacarpal bone, cystlike areas in the mandibles, punched-out areas in the skull, and "a prominence of markings" in the lung fields. In the aspirate from the hand lesion acid-fast bacilli were demonstrated. Therapy of 0.25 gm. of streptomycin every six hours and 0.5 gm. of Promizole was instituted. The clinical course was that of general improvement and healing of the lesions. After five months of therapy the hand was healed and the other lesions were only dimly seen in the roentgenograms; therapy ceased at six months. The leukocytes then numbered 8,700 with a shift from 50 to 72 per cent lymphocytes. At 30 months of age the child continues to be well. No eighth nerve damage has been noted.—*Osteitis tuberculosa multiplex cystica: Its Treatment with streptomycin and Promizole, M. Torkish, J. W. Murphy, P. Roody, & R. Saigh, J. Pediat., November, 1949, 35: 625.*—(*W. H. Oatway, Jr.*)

Bone and Joint Tuberculosis.—Streptomycin treatment makes it possible to perform operative measures for active tuberculous infections of bones and joints much sooner than otherwise could be done, thus preventing long periods of invalidism and extensive destruction of the joints. Tuberculous abscesses and sinuses heal promptly under the influence

of streptomycin, provided the primary focus is dealt with surgically at the same time. The final evaluation of streptomycin treatment in conjunction with surgical procedures should be deferred until longer follow-up periods become available. Chronic, less active tuberculous lesions of bones and joints do well with surgical treatment alone and streptomycin should not be used in these cases.—*Streptomycin combined with surgery in the treatment of bone and joint tuberculosis, A. D. Smith & H. I. Yu, J. A. M. A., January 7, 1950, 142: 1.—(H. Abeles)*

Tuberculosis of Ureter.—Six patients with tuberculous lesions of the kidneys and long-standing involvement of the ureters were treated with streptomycin. In 5 patients the ureter became occluded or impassable. This is probably a manifestation of the healing process promoted by streptomycin therapy. Such obstructions of the ureter may mislead the clinician by causing falsely negative bacteriologic examinations of the bladder urine, due to exclusion rather than to healing of the tuberculous lesion. In addition to making continuous tests for bacteria during and after treatment, one must also determine whether or not the urine from the tuberculous kidney is reaching the bladder.—*Clinical response of the tuberculous ureter to streptomycin therapy, J. R. Rinker, J. A. M. A., January 14, 1950, 142: 87.—(H. Abeles)*

Extrapleural Pneumothorax and Streptomycin.—Fluid containing tubercle bacilli appeared in 37 patients with extrapleural pneumothorax. They were treated with streptomycin, 1.0 gm., injected daily into the extrapleural space for twenty consecutive days, followed by 1.0 gm. given intramuscularly each day for an additional fifteen to twenty days. In 33 of the 37 patients, the air pocket became completely dry. In 2 other patients, a few cubic centimeters of sterile fluid persisted. The treatment failed in 2 cases.—*Résultats du traitement des épanchements bacillifères extrapleuraux par la streptomycine, R. Legendre & A. Gugelot, Rev. de la tuberc., 1949, 13: 977.—(V. Leites)*

Incubation Period of Tuberculosis.—Guinea pigs were infected with a standard inoculum of a streptomycin-sensitive strain of human tubercle bacilli grown for six days on Sauton's medium. Streptomycin treatment was started coincidentally with the inoculation in one group, was begun fourteen days after the inoculation in another group, and was never given to the control group. The incubation period was determined by conversion to positive of the Mantoux test performed with 0.1 cc. of a 1:10 dilution of Koch's Old Tuberculin injected intracutaneously. The incubation period was prolonged in the streptomycin-treated animals, perhaps because of the arresting influence of the streptomycin on the tubercle bacilli. As the animals became tuberculin-positive after a long interval, the bacilli may have become resistant to streptomycin during the experiment. The incubation period was unaltered by the streptomycin when the inoculation was made with a streptomycin-resistant strain.—*The influence of streptomycin on the incubation period of tuberculosis, G. Olsen-Boje & L. Rudback, Acta tuberc. Scandinav., 1949, Supplement 21: 88.—(K. T. Bird)*

Streptomycin Resistance.—After inoculation with streptomycin-sensitive tubercle bacilli of the human strain, 18 guinea pigs were treated with streptomycin 2.5 to 20 mg. daily for three months. No increase in streptomycin resistance could be detected in the tubercle bacilli obtained from the diseased organs. When guinea pigs were inoculated with resistant strains, the resistance was found to persist after animal passage. Streptomycin was ineffective in these animals even in daily doses of 20 mg. Animals injected with streptomycin-dependent strains showed rapid progression of their disease after streptomycin administration. In another series of experiments, guinea pigs were inoculated with a mixture of streptomycin-sensitive and

-resistant strains. One group of animals was treated with daily doses of 2.5 to 20 mg.; the other group was left untreated. The lesions were equally severe and extensive in the treated and untreated animals. In the untreated group equal parts of sensitive and resistant strains were found in all involved organs. In the animals treated with high doses only the resistant strains penetrated into the various organs without modification of the initial degree of streptomycin resistance. —*Repartition des bacilles plus ou moins résistants à la streptomycine selon les organes et le type de la lésion dans la tuberculose expérimentale du cobaye: Action des traitements par l'antibiotique, F. Tison, Ann. Inst. Pasteur, December 1949, 77: 767.*—(*V. Leites*)

Streptomycin Sensitivity.—The growth of tubercle bacilli from a given patient was determined on a medium consisting of his own blood drawn at a time during streptomycin treatment when the level of the antibiotic was highest. By the micro-culture method, slides of sputum were incubated in the citrated blood of the patient. This simple method requires no preparation of media and determines streptomycin resistance within a few days, the resistance being correlated with the maximum blood concentration of the drug in that patient. The procedure has certain defects inherent in the slide culture method. The failures are most often due to the small number of living bacilli in some specimens. Cultures were grown in blood before and during streptomycin therapy in 60 cases. Some patients who had never received streptomycin previously had resistant strains on the second day of treatment. The blood concentration of streptomycin in all cases was higher than that effective against sensitive strains.—*La sensibilité à la streptomycine du bacille tuberculeux étudiée par la microculture sur lames dans le sang des malades en traitement, É. Bernard & B. Kreis, Rev. de la tuberc., 1949, 13: 50.*—(*V. Leites*)

Streptomycin Resistance.—To determine the streptomycin resistance of tubercle bacilli *in vivo*, guinea pigs are inoculated intradermally with 0.1 mg. of bacilli and treated with 20 mg. of streptomycin daily. The reactions at the site of inoculation are compared with those of an untreated control group. If "total resistance" is present, the cutaneous lesion is as voluminous and extensive as in the controls. If the bacilli have "partial resistance" the lesion is smaller and appears later. The results obtained with this method are comparable to those obtained with the usual *in vitro* determinations. The technique is not considered of any practical importance for clinical purposes but it provides a valuable means of experimentation for investigating the mechanism of action of streptomycin.—*Sur l'étude de la streptomycino-resistance du B. tuberculeux par la méthode de l'inoculation intradermique au cobaye et ses enseignements, É. Bernard & B. Kreis, Ann. Inst. Pasteur, December 1949, 77: 764.*—(*V. Leites*)

Streptomycin Resistance.—When tubercle bacilli obtained from patients treated with streptomycin were tested for streptomycin sensitivity on Youman's medium, new cultures appearred between the fifteenth and thirtieth days in 58.4 per cent of the 65 analyzed cases. The appearance of isolated colonies was even more frequently observed (84.6 per cent of cases). These cultures or colonies represent resistant variants of the bacillus which grow late. The establishment of this slow growth may reveal the mode of emergence of resistance to streptomycin. It has no practical influence on the technique of titration except that in the future solid streptomycin media may become of increasing importance. (Authors' summary).—*Sur l'apparition tardive de variantes bacillaires résistantes au cours du titrage de la streptomycinosensibilité du bacille tuberculeux, G. Canetti & A. Saenz, Ann. Inst. Pasteur, November 1949, 77: 611.*—(*V. Leites*)

Aureomycin for Bronchiolitis.—No specifically effective therapy has been available for acute bronchiolitis or "viral" pneumonitis of infants. There is usually an interstitial

inflammation with some emphysema and atelectasis and the bacteriology is nonspecific. The symptoms have an insidious onset followed by an acute, severe illness with labored and obstructed respiration. Sixty-four cases are reported, of which 32 received aureomycin, 50 mg. per kg. by mouth in the first few cases, 100 mg. in the later ones. Alternate cases received penicillin, sulfadiazine, streptomycin, or combinations of them. Of the aureomycin-treated series, the patients with white blood counts below 15,000 and those with rising cold-agglutinin titers had an appreciably greater chance of beconing afebrile in 24 hours. They were also hospitalized an average of three days less than the patients without these findings. The drug was not seriously toxic.—*Aureomycin in the treatment of acute bronchiolitis of infants, B. F. Thompson, Jr. & S. Spector, J. Pediat., November, 1949, 35: 546.*—(*W. Oatway, Jr.*)

Aureomycin for Influenza.—Aureomycin was used in the treatment of a miscellaneous group of 41 cases of severe, acute respiratory infections with or without pneumonia. Infection with *H. influenzae*, Type A, was proved in 18 patients, associated in most instances with bronchopulmonary involvement; the administration of aureomycin by mouth was followed by prompt defervescence and alleviation of symptoms, the pulmonary lesions clearing rapidly. Pathogenic bacteria of possible significance were isolated from throat or sputum cultures only in a few of those patients in whom pulmonary lesions could not be demonstrated roentgenographically. Similar rapid improvement occurred during aureomycin therapy in 10 patients with severe, acute respiratory infections without pneumonia. Three of these patients had nasopharyngitis and exudative tonsillitis associated with beta hemolytic *Streptococci* but no etiologic agent was identified in the others by the bacteriologic or serologic methods employed. In 5 patients with classical signs and symptoms of lobar pneumonia but in whom bacteriologic studies failed to reveal the etiologic agent, aureomycin administration was likewise accompanied by a rapid termination of the acute disease. Each of the remaining 8 patients had pneumonia as a complication of other serious conditions and no microbial agent could be identified as the cause of the pneumonia. The results of aureomycin therapy in these cases were equivocal. (Authors' summary)—*Aureomycin in the treatment of influenza and certain other acute respiratory infections with or without pneumonia, M. Finland, E. B. Wells, H. S. Collins, & T. M. Gocke, Am. J. Med., January, 1950, 8: 21.*—(*T. H. Noehren*)

Pneumococcal Pericarditis.—Pericarditis is one of the dreaded complications of lobar pneumonia and pneumococcal septicemia and may occur as the terminal episode of any pneumococcal infection. The mortality rate has been between 50 and 100 per cent, although pneumococcal pericarditis is a comparatively rare complication. During three years, 6 patients were treated with intramuscular penicillin as well as repeated pericardial paracenteses and intrapericardial instillation of penicillin. Intramuscular penicillin was continued until the pneumonia resolved, and the intrapericardial administration was stopped when pus was no longer present in the aspirated fluid. Of the 6 patients, 3 were cured and 3 succumbed to the infection. Only one patient required supplementary surgery and this patient died of cardiac failure.—*Penicillin treatment of pneumococcal pericarditis, H. L. Chung, Chinese Med. J., August, 1949, 67: 430.*—(*B. Hyde*)

LABORATORY STUDIES

Segmental Physiology.—The importance of maintaining the cough reflexes, of avoiding restriction of the chest motion by tight strapping, and of administering gas under tension is now recognized in the treatment of generalized pulmonary edema. The function of the bronchiolar musculature in trapping alveolar air to increase pressure for combatting localized pulmonary edema is just being studied. Observations on the Kartagener syndrome

(bronchiectasis, situs inversus and agenesis of the accessory sinuses) suggest that the bronchiectasis may be secondary to an altered secretory activity of the epithelium of the respiratory tract. Two children were observed with situs inversus and agenesis of the sinuses but without bronchiectasis; large quantities of mucous secretion were produced by cough and nasal discharge. In many cases a diseased segment remains inflated by trapped air after deflation of the remainder of the lobe, because of an obliterative bronchitis and bronchiolitis which also may or may not be accompanied by true bronchiectasis. This may be significant in the development of certain types of bronchiectasis since it favors retention of secretions in the larger bronchi. It is known that both capillary blood and interalveolar air may drift between segments, a phenomenon unique to the lung, which appears designed to preserve the volume even though the respiratory function of a segment is destroyed.—*The segmental and lobular physiology and pathology of the lung, E. Churchill, J. Thoracic Surg., June, 1949, 18: 279.*—(*R. E. MacQuigg*)

Fluoromicroscopy of Tubercle Bacilli.—The advantages of Hagemann's method for the fluoromicroscopic demonstration of tubercle bacilli include an increased incidence of positive results, better contrast with less visual strain, easier detection of bacilli in a large field, and saving of time and effort. Auramine has proved to be the best dye for fluorescent microscopy in spite of the poor lasting quality of its solutions in tropical climates. Examination should be made in a dark room or by a dim light. The method may be used for the examination of urine, fecal, gastric, and spinal fluid specimens, and even for histologic sections.—*O. diagnóstico do "Mycobacterium tuberculosis" pela fluoromicroscopia, K. Arens, Rev. brasil. de tuberc., July-August, 1949, 17: 393.*—(*A. A. Moll*)

Culture of Tubercle Bacilli.—The usual culture methods have been modified as follows to make them more sensitive, with a better distribution of colonies and an extremely low incidence of contamination: (*1*) 2 cc. of sputum are mixed with 8 cc. of 4 per cent sodium hydroxide and covered with 100 cc. (*2*) After incubation for thirty minutes at 37°C., 70 cc. of 0.35 per cent sulfuric acid are added. Approximate neutralization is thus obtained. The adding of a colored reagent should be avoided in order to minimize contamination. (*3*) Centrifugation is performed for thirty minutes at 3,000 r.p.m. This has no unfavorable effect on the bacilli. (*4*) The sediment is diluted in a sterile water-glycerine mixture. (*5*) Löwenstein's medium as modified by Jensen is used as the most sensitive and reliable.—*Perfectionnements aux procedés usuels de culture du bacille de Koch à partir des produits surinfectés, F. Tison, Ann. Inst. Pasteur, September 1949, 77: 313.*—(*V. Leites*)

Flora of Bronchial Secretions.—In the course of routine bronchoscopic examinations of 100 patients, cultures were made of the bronchial secretions. Ninety-five per cent of the patients had either tuberculosis, cancer, tracheobronchitis, bronchiectasis, abscess, delayed resolution of pneumonia, or collapsed lung. There were 122 strains of aerobic organisms recovered. These were mainly cocci, of which most were *Streptococci*. Pneumococci were found 17 times but never in cases of delayed resolution. Seven of 11 cultures from bronchitis cases were sterile. The only rod seen frequently was *H. influenzae* which was identified especially often in cases of tumor and collapse. Anaerobic cultures also were made. In 14 cases, these revealed facultative organisms not shown by aerobic methods. In 11 cases, obligate anaerobic cocci were cultured. Two types of anaerobes were common, *V. alcalescens*, which is large and insensitive to penicillin, and *Strep. parvulus* which is small and sensitive. *Clostridia* were never recovered.—*The flora of 100 bronchial secretions, J. G. Benstead, Lancet, February 4, 1950, 1: 206.*—(*A. G. Cohen*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Diagnositic BCG Test.—A group of healthy, tuberculin-negative persons theoretically may comprise at least 5 categories: (*1*) persons not exposed to tuberculous infection and consequently not infected; (*2*) persons exposed but not infected, due to special powers of resistance; (*3*) persons who have become infected but who for some reason have not developed cutaneous sensitivity to tuberculin; (*4*) persons who have been infected and retain viable bacilli but whose tuberculin sensitivity has disappeared; and (*5*) persons who have been infected, who have undergone a reversal of the tuberculin reaction, and in whom the disease has been cured. Through immunity tests it should be theoretically possible to distinguish between Groups (*1*) and (*5*), on the one hand, and Group (*4*) on the other. Groups (*2*) and (*3*) may be presumed to occur rarely, if at all, in practice. Cutaneous BCG vaccination of tuberculin-negative individuals, presumptively not previously infected, produces a local reaction generally appearing after twelve to twenty days. If tuberculin-positive subjects are inoculated with BCG, the local reaction appears much sooner. Distinct formation of papules after six days indicates such a specific accelerated reaction. A modification of the Rosenthal-Birkhaug technique, using 20 mg. of BCG per ml., is well suited for the study of this local reaction. This test was employed on about 500 subjects, some of whom were Pirquet-positive, some Pirquet-negative but Mantoux-positive, while some were negative both to Pirquet and Mantoux tests. Without furnishing conclusive proof, the results support the hypothesis that an accelerated-reaction to BCG in tuberculin-negative persons is an indication of active tuberculous infection. For example, it was anticipated that an accelerated reaction would be positive, as it was in 54 of the 66 tuberculin-negative subjects in the older age group (over 50 years). These were, in all probability, persons who had been infected with tubercle bacilli but who had lost their sensitivity to tuberculin; their bacilli may be supposed to be still living. It may be imagined that an infected individual who is not constantly exposed to super-infection may pass through the following stages: a vesicular Pirquet reaction immediately after infection; a weakening Pirquet reaction over the years until there is a negative Pirquet reaction but a positive Mantoux test; then a gradually weakening Mantoux reaction, but an accelerated reaction to BCG; and finally a loss of the accelerated reaction when the infection is completely healed. The BCG test ought to be further employed in individuals who show tuberculin negativity after BCG vaccination. It should be determined by means of such follow-up investigations whether an accelerated reaction to BCG constitutes a sufficient criterion of attained immunity. Finally, this test may be used to distinguish between specific and nonspecific Mantoux reactions in individuals who are Pirquet negative but Mantoux positive.—*Diagnostic BCG test, H. J. Ustvedt & A. Aanonsen, Acta tuberc. Scandinav., 1949, 23: 1.*—(*K. T. Bird*)

BCG Vaccination.—It has been demonstrated conclusively that increased resistance to infection with virulent tubercle bacilli is produced through BCG vaccination. However, this resistance is not complete. The value of BCG vaccination has to be assessed in the light of the pathogenesis and changing epidemiology of tuberculosis. In 1945 deaths from tuberculosis in persons less than 15 years of age accounted for only 3 per cent of all such deaths in New York City, while 61 per cent occurred among persons over 40 years of age. In adults over 40 years of age, especially in men, both minimal pulmonary tuberculosis and deaths from tuberculosis are caused in large part by reinfection after a previous infection has healed. In spite of a natural vaccination with virulent tubercle baccilli, a new progressive disease may develop. Tuberculosis cannot be effectively controlled until the problem of tuberculous reinfection has been met. It is extremely doubtful that artificial vaccination can produce

results superior to natural vaccination with small numbers of living virulent tubercle bacilli, and yet natural vaccination fails to control the disease. Greater emphasis should be given to the major problems in tuberculosis, namely, unrecognized tuberculosis and that due to reinfection in adults over 40 years of age.—*Prophylactic (BCG) vaccination to control tuberculosis, E. M. Medlar, J. A. M. A., October 29, 1949, 141: 593.—(H. Abeles)*

BCG Vaccination in Allergic Individuals.—At S. Paulo an extensive study was conducted to test the safety of BCG vaccination in tuberculin-positive individuals. The two groups of subjects each included persons of both sexes and of various ages, mostly six to twenty-nine years old. The first group was made up of inmates in a home for the blind, where freedom from tuberculosis was ascertained by repeated examinations. The second group consisted of close relatives of patients attending a dispensary. The first group contained 256 persons, 120 of whom reacted to tuberculin; 99 of these were inoculated with BCG vaccine and 21 were retained as controls. The second group consisted of 295 persons in families; 259 of them gave positive reactions to tuberculin. Of these, 140 were inoculated with BCG vaccine, the other 119 being kept as controls. The 136 anallergic individuals in the first group were also given BCG. The dosage of BCG ranged from 0.20 gm. in a single dose to 3.60 gm. divided into weekly or monthly doses of 0.20 gm. each. The first group was followed for at least one year and ten months after the last administration of BCG and the second group for five months to two years. Roentgenographic and bacteriologic examinations were made throughout this period. In neither of the two allergic groups was any sign of tuberculosis ever detected. Among 94 controls in the second group, 2 proved cases of tuberculosis developed. Nontuberculous diseases showed a similar incidence and course among vaccinated allergic persons and unvaccinated controls. Tuberculin sensitivity definitely was attenuated in the vaccinated persons, especially when weekly or monthly doses were used. While the data are not yet conclusive, it seems that BCG is not only harmless in healthy allergic individuals but may confer a degree of protection. These results and previous experience in Brazil make it likely that Calmette's method may be used in individuals of all ages without resort to the present measures for selecting prospects.—*Resultados da vacinacão BCG no Brasil, J. Rosemberg, Rev. brasil. de tuberc., July-August, 1949, 17: 331.—(A. A. Moll)*

Nonuniformity of Tuberculin.—The reactions to 3 batches of tuberculin were compared in guinea pigs with experimental tuberculosis and in tuberculous patients. The substances were found to vary in the speed and intensity of the skin reactions which they produced. There were also differences in the degree of nonspecific responses. The necessity for standardized tuberculin is stressed.—*Variations des réactions cutanées chez les sujets allergiques selon les tuberculines employés, P. Davy & F. Tison, Rev. de la tuberc., 1949, 13: 762.—(V. Leites)*

Value of Routine Roentgenograms.—The common criticisms of routine roentgenographic examinations are based on their low yield and high cost. Yet, in 1948, 36 per cent of all patients admitted to the Student's Sanatorium, St. Hilaire, France, were discovered to be tuberculous by routine roentgenography. It has been stated also that mass surveys find mostly inactive cases with no tendency towards progression and no need for treatment. Therefore, an analysis was made of the disease's activity and course in 329 tuberculous patients first discovered by routine examination. Of these, 76 (23 per cent) had symptoms suggestive of active disease which should have led them to seek medical advice prior to the routine roentgenogram. Subsequently 79 per cent of this group showed signs of activity, whereas 21 per cent remained stationary. Another 172 patients (69 per cent) had latent disease and

were asymptomatic; in 74 per cent the roentgenographic findings demonstrated the activity of the tuberculous process. Of the entire group of patients, the remaining 46 were asymptomatic and had radiologically benign lesions. Of these 38 showed signs of active disease while under observation, with roentgenographic progression and the appearance of a positive sputum in 6 cases. On the whole, the gravity of subsequent progression of disease was equal for the "attenuated" and the more serious forms. Cavity formation occurred with the same frequency in the two groups.—*Prognostic des tuberculoses pulmonaires décelées per examen systematique, R. Cohen & J. Palles, Rev. de la tuberc., 1949, 13: 987.—(V. Leites)*

Routine Examinations and Prognosis.—Of 565 patients from the French Navy admitted to sanatoriums between 1946 and 1949, 140 (25 per cent) had been discovered to be tuberculous by routine roentgenography. The course of disease of this group was compared to the course in the remaining patients. The average age of both groups was 25 years. The incidence of cases with favorable prognosis was higher in the group discovered routinely. Only 1.6 per cent of cases diagnosed on routine examination had poor prognosis as compared to 11 per cent among the remaining patients. Surgical treatment was necessary in a smaller percentage of patients discovered on routine roentgenography and their stay in the sanatorium was of shorter duration than that of patients admitted because of symptoms.—*Le devenir en milieu sanatorial des tuberculoses decelées par le depistage radiologique systematique (étude statistique portant sur 565 dossiers du personnel de la marine nationale), Audoye, Constans, Manquene, & Pilon, Rev. de la tuberc., 1949, 13: 943.—(V. Leites)*

Compulsory Isolation for Tuberculosis.—Forcible isolation of asocial tuberculous patients is practiced in Russia and the practice has been submitted to a popular referendum in Switzerland. The author asked 100 sanatorium patients and 300 other persons whether they favored forcible isolation of infectious individuals if adequate financial care were provided for dependents. Only 14 of the 300 outsiders were opposed as were 11 of the 100 sanatorium patients. The replies appeared to be affected by political leanings but a similar referendum in The Netherlands would probably receive unequivocal approval. —*Verplichte opneming in T.B.C.-Sanatoria ?, P. G. op de Coul, Tijdschr. v. sociale geneeskunde, August 28, 1949, 27: 155.—(J. van der Vate)*

Attack Rate in Contacts.—While there is abundant evidence that the incidence of both tuberculous infection and disease has declined in recent years, there have been no reports that the attack rate among the associates of patients with infectious tuberculosis has diminished. Among 432 contacts of patients with infectious tuberculosis in Cattaraugus County, New York, the attack rate has declined from 78 to 51 between 1929–1934 and 1941–1946. It has been found that the incidence of positive tuberculin reactions is greater in household associates of women, young persons, and patients with advanced diseases than among the contacts of men, older persons, and patients with minimal tuberculosis. The reduction in the attack rate of household associates of infectious patients in recent years is attributed to the greater proportion of minimal infections among these patients, as well as a reduction in the number of young persons and women in the infectious group.—*Apparent decline in tuberculous infection among household associates of sputum-positive cases of tuberculosis, W. R. Ames & H. C. Miles, Am. J. Pub. Health, February, 1950, 40: 143.—(M. B. Lurie)*

Morbidity in Tuberculosis Contacts.—At the Belo Horizonte Dispensary in Brazil, the contagiousness of tuberculosis has been studied in a series of 1,874 persons varying in age from less than a year to over 46 years. The incidence of tuberculosis among these con-

tacts was 13.9 per cent, the rate ranging from 27 per cent in the group less than three years of age to 5.3 per cent in persons over 46 years old. The outstanding sources of infection were parents, especially in contacts from the youngest group, brothers, spouses, and children. Conjugal contacts showed a morbidity rate very similar to that of adults exposed otherwise. Exposure in the home proved to be 3.5 times as hazardous as exposure outside it. Degree of kinship did not seem to influence the rates of infection in individuals exposed to household contagion. In opposition to findings by United States workers, the 4- to 14-year age group showed a high morbidity rate (12.5 per cent), exceeded only by the group less than three years old and the 15- to 30-year age group.—*Principais fatores responsáveis pela morbidade nos contactos de tuberculose, J. Feldman, Rev. Rev. brasil. de tubere., July–August, 1949, 17: 357.*—(*A. A. Moll*)

Tuberculosis in Brazil.—The latest official data (1936–1945) show that all but one of the 21 capital cities of Brazilian states, even those with comparatively low death rates, are now in the midst of a period of widespread tuberculosis. The exception is S. Paulo with a tuberculosis death rate of about 100 per 100,000 since the end of the last century. Only three other cities have rates under 100; four have rates from 100 to 300; and the other thirteen, from 300 to 500 per 100,000. Nine in this last group are, however, beginning to reveal signs of regression. The contrast between the two largest cities in the country, S. Paulo and Rio de Janeiro, is striking. In S. Paulo, decreasing rates have been apparent since 1894. This is the only Brazilian city and one of the four South American cities now in the final endemic stage of the disease, Buenos Aires, Rosario, and Montevideo being the others. These four communities have in common a Spanish or Italian population. On the other hand, the tuberculosis mortality in Rio de Janeiro has hovered around 300 per 100,000 since the beginning of the century. The latter city has basically a Portuguese population with accessions from rural areas. In one Rio de Janeiro hospital, 70 of each 100 persons dying there were from outside the city; 40 per cent of these 70 had recent primary tuberculosis. One outstanding fact in Brazil, as in other South American countries, is that much lower rates prevail in the interior, as compared to the seashore areas.—*Epidemiologia da tuberculose (Aposicao do Brasil), R. Fernandes, Clin. tisiol., October–December, 1949. 4: 423.*—(*A. A. Moll*)

Tuberculosis in Mental Defectives.—The attack rate and the incidence of clinical tuberculosis was studied in a school for mentally defective children with 2,700 students during 1937 to 1948. During these twelve years there were three distinct periods. The first, 1936–1938, was characterized by high conversion rate to tuberculin sensitivity and a corresponding high incidence of development of clinical tuberculosis. At this time there was no adequate segregation of patients with active disease. During the second period of seven years, 1939–1946, both the attack rate and the number of clinically active cases were greatly reduced and remained at a relatively constant level. During this period there was more effective isolation. In 1946 a single case of active tuberculosis was introduced into this community with a resulting great increment in the attack rate and the incidence of active disease.—*Tuberculosis in a school for mental defectives, R. E. Plunkett, J. Katz, M. E. Thompson, & R. R. Donk, Am. J. Pub. Health, August, 1949, 39: 1016.*—(*M. B. Lurie*)

Pneumoconiosis and Tuberculosis in Dockers.—Of 100 men who worked on docks handling grain, seed, and chemical cargos, 71 were found to have abnormal chest roentgenograms when referred to a chest clinic. Chemical examination of the dusts to which these workers were exposed revealed silica and soluble silica, "in sufficient amounts to produce pneumoconiosis." Twenty-two of the 100 workers were found to have pneumoconiosis with reticulation, fibrosis, or mottling on the

chest roentgenogram. In addition, 36 cases of tuberculosis with bacteriologically positive sputum and 7 with negative sputum were seen. The chief complaint of these patients was shortness of breath; not cough, sputum, weight loss, or fatigue. Three workers were found to have bronchogenic carcinoma and in 3 other cases the cause of the diffuse pulmonary fibrosis could not be established as being either pneumoconiosis or tuberculosis. —*Pneumoconiosis and tuberculosis in dockers dealing with grain and seeds, L. Dunner, Brit. J. Radiol., December, 1949, 22: 717.*—(*B. Hyde*)

Silico-tuberculosis.—Silicosis seems to be the only one of the pneumoconioses causing an increased prevalence of tuberculosis, and tuberculosis seems to be the only infection which silicosis affects adversely. In a survey of over 15,000 workers in dusty trades, active tuberculosis was found among 3 per cent of the persons with silicosis and among 0.3 per cent of those without silicosis. There was an additional group of over 400 persons (19 per cent of those with silicosis) who had confluent shadows demonstrated roentgenologically in whom tubercle bacilli could not be demonstrated in the sputum at the original examination. Many of them have been studied over a period of fifteen years and a considerable number of cases of active tuberculosis have developed in this group. The deleterious effect of silicosis seems to be largely on preexisting tuberculous foci and relatively infrequently as a predisposing factor to new tuberculosis. Tuberculosis control measures in the community are helping to prevent new cases of silico-tuberculosis to such an extent that it soon will cease to exist as an occupational hazard.—*Pneumoconiosis and infection, O. A. Sander, J. A. M. A., November 14, 1949, 141: 813.*—(*H. Abeles*)

Coccidioidin Patch Tests.—Two types of ointment and one type of coccidioidin-impregnated filter paper have failed to produce results comparable to the tuberculin patch test. The former produced only 4 per cent and the latter 22.5 per cent positive reactions among individuals known to be reactive to intradermal coccidioidin. The reason for failure is not apparent.—*A coccidioidin patch test, R. Cohen & M. A. Gifford, J. Pediat., November, 1949, 35: 601.*—(*W. H. Oatway, Jr.*)

Silent Pulmonary Carcinoma.—The average patient with pulmonary carcinoma waits three months after the onset of symptoms before seeking medical advice. There is another seven months' delay with the orthodox methods physicians use to sort out patients with cancer of the lung from those with other conditions. The reasons for this delay are: (*1*) the symptoms are not unusual; (*2*) physical examination is unreliable; (*3*) secondary infection disguises the primary disease frequently; and (*4*) the roentgenologic findings are variable. Cancer of the lung has a silent phase and is detectable. Small tumors growing in the periphery will cast a direct shadow. Smaller tumors centrally located cause a segmental or subsegmental bronchial obstruction, which will cast a shadow of the corresponding atelectatic segment. On the basis of the Minneapolis mass survey, it is expected that 10 primary cancers of the lung will be found for every 100,000 persons examined. It is impossible to say how often people should be screened in order to give reasonable protection from cancer of the lung. For the present, selective screening on an annual basis would seem to be wise. Prompt and adequate investigation of suspects is equally important.—*Silent phase of cancer of the lung, R. H. Overholt & I. C. Schmidt, J. A. M. A., November 19, 1949, 141: 817.*—(*H. Abeles*)

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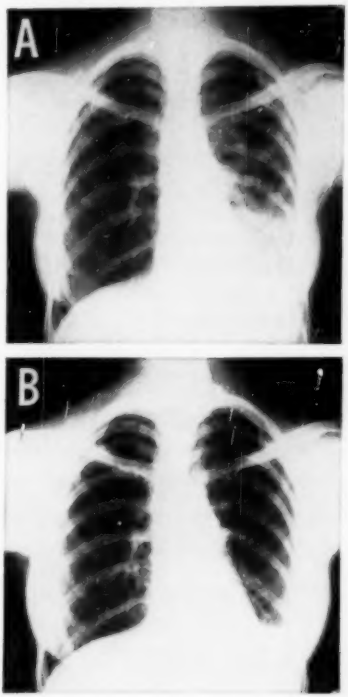

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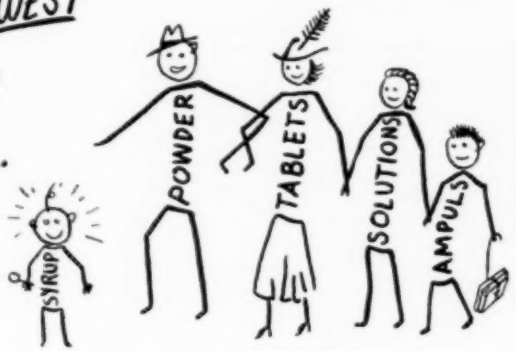

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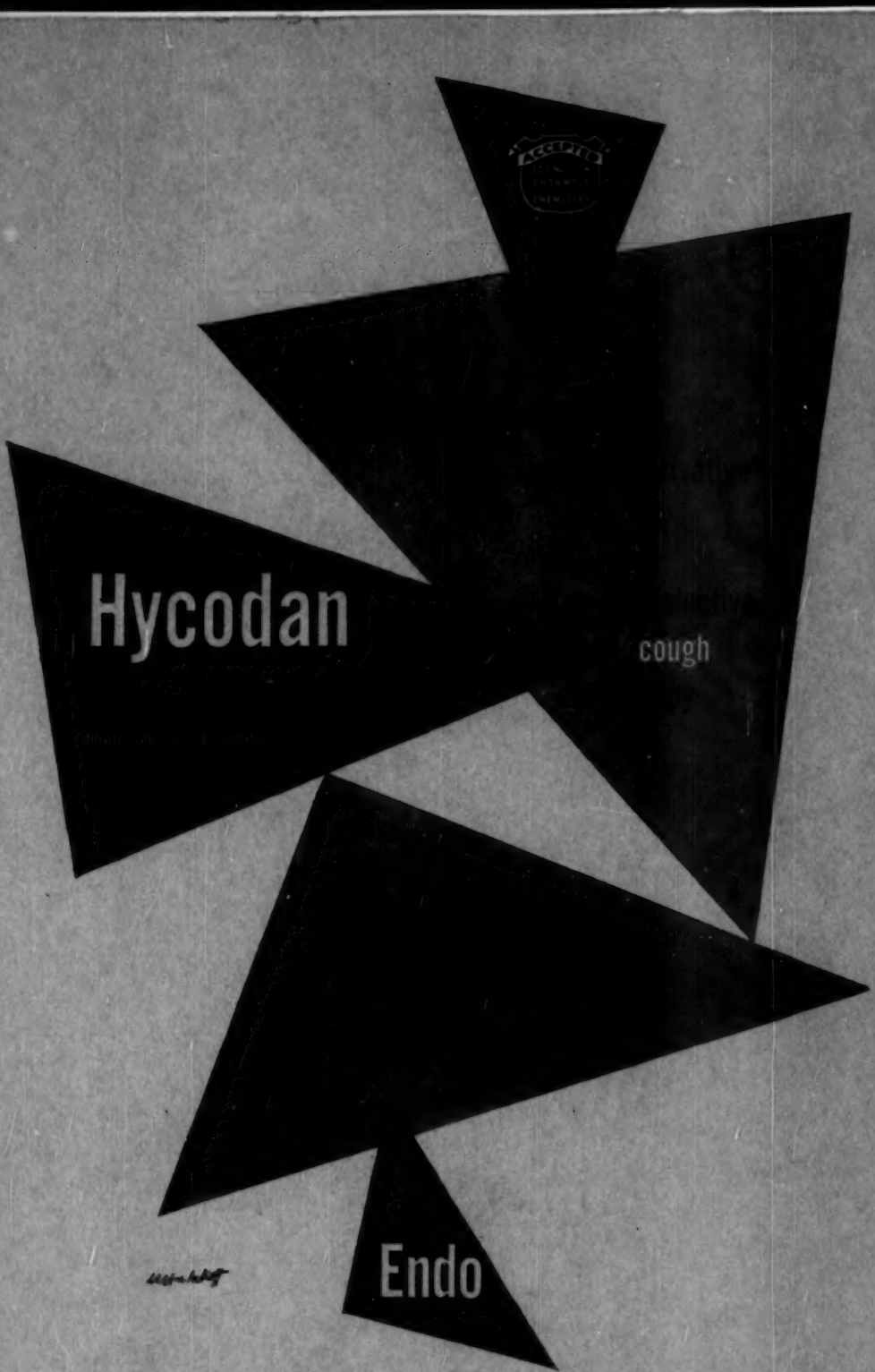
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